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Ontario

SPIELBERG

# ROYAL COMMISSION OF INQUIRY INTO CERTAIN DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND RELATED MATTERS.

In Ch: PSAL

Hearing held
8th floor
180 Dundas Street West
Toronto, Ontario

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| **The Honourable Mr. Justice S.G.M. Grange** | Commissioner |
| **P.S.A. Lamek, Q.C.** | Counsel |
| **E.A. Cronk** | Associate Counsel |
| **Thomas Millar** | Administrator |

Transcript of evidence
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ROYAL COMMISSION OF INQUIRY INTO CERTAIN DEATHS AT THE HOSPITAL FOR SICK CHILDREN AND RELATED MATTERS.

Hearing held on the 8th Floor, 180 Dundas Street West, Toronto, Ontario, on Monday, the 24th day of October, 1983.

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| THE HONOURABLE MR. JUSTICE S.G.M. GRANGE | - Commissioner |
| THOMAS MILLAR | - Administrator |
| MURRAY R. ELLIOT | - Registrar |

APPEARANCES:

| | |
|---|---|
| P.S.A. LAMEK, Q.C. )<br>E. CRONK ) | Commission Counsel |
| D. HUNT )<br>L. CECCHETTO) | Counsel for the Attorney General and Solicitor General of Ontario (Crown Attorneys and Coroner's Office) |
| I.G. SCOTT, Q.C.)<br>I.J. ROLAND )<br>M. THOMSON )<br>R. BATTY ) | Counsel for The Hospital for Sick Children |
| D. YOUNG | Counsel for The Metropolitan Toronto Police |
| W.N. ORTVED | Counsel for numerous Doctors at The Hospital for Sick Children |
| F. KITELY | Counsel for the Registered Nurses' Association of Ontario and 35 Registered Nurses at The Hospital for Sick Children |

(Cont'd)

APPEARANCES (Continued):

| | |
|---|---|
| D. BROWN | Counsel for Susan Nelles - Nurse |
| E. FORSTER | Counsel for Phyllis Trayner - Nurse |
| J.A. OLAH | Counsel for Janet Brownless - R.N.A. |
| B. JACKMAN | Counsel for Mrs. M. Christie - R.N.A. |
| S. LABOW | Counsel for Mr. & Mrs. Gosselin, Mr. & Mrs. Gionas, Mr. & Mrs. Inwood, Mr. & Mrs. Turner, and Mr. & Mrs. Lutes (parents of deceased children) |
| F.J. SHANAHAN | Counsel for Mr. & Mrs. Dominic Lombardo (parents of deceased child Stephanie Lombardo); and Heather Dawson (mother of Amber Dawson) |
| W.W. TOBIAS | Counsel for Mr. & Mrs. Hines (parents of deceased child Jordan Hines) |

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## INDEX of WITNESSES



## INDEX of EXHIBITS

A/BN/ak

---Upon commencing at 10:00 a.m.

THE COMMISSIONER: Yes, Mr. Lamek?

MR. LAMEK: Mr. Commissioner, may I call this morning, please, Dr. Stephen Spielberg.

THE COMMISSIONER: Thank you.

DR. STEPHEN PAUL SPIELBERG, Sworn

DIRECT EXAMINATION BY MR. LAMEK:

Q. Dr. Spielberg, you are a member of the staff of the Hospital for Sick Children in the Division of Clinical Pharmacology, I believe?

A. Yes, that is correct.

Q. And you are also a member of the Research Institute at the Hospital?

A. Correct.

Q. And you hold an appointment as an associate professor in the Departments of Pediatrics and Pharmacology at the University of Toronto?

A. Yes, that is right.

Q. Briefly, Doctor, with respect to your background, you hail from New York City?

A. Yes.

Q. And you did your undergraduate work at Princeton, I believe, where you majored in biology and from which university you were graduated

Magna Cum Laude earning in the process a Phi Beta Kappa?

A. That is right.

Q. And thereafter you attended the University of Chicago where you earned what in military terms would be called a doctorate with bar, that is to say, a Ph.D. in pharmacology in 1971, and an M.D. in 1973?

A. Yes.

Q. Thereafter, you did an internship and a junior assistant residency from June of 1973 until June of 1975 at the Children's Hospital Medical Centre in Boston where you specialized in pediatrics, did you not?

A. Correct.

Q. And you were a clinical fellow in pediatrics at the Harvard Medical School?

A. Correct.

Q. You then spent two years in the U.S. Armed Forces, holding a commission and working, as I understand it, in the U.S. Public Health Service?

A. Yes.

Q. And then from 1977 until 1981 you were at Johns Hopkins University, School of

Medicine initally, I believe, as an instructor, and latterly as an assistant professor in the Division of Clinical Pharmacology in the Departments of Pediatrics, and Pharmacology and Experimental Therapeutics?

A. That is right.

Q. And you were also a member of the active pediatrics staff at the Johns Hopkins Hospital, were you not?

A. Yes.

Q. And then in July of 1981 you came to Canada to take up the appointments which you now hold at the Hospital for Sick Children and the University of Toronto?

A. Yes.

Q. Now, Dr. Spielberg, you hold memberships in professional societies, including the Canadian Society for Clinical Pharmacology, and you are a member of the Committee on Drugs of the American Academy of Pediatrics, I believe?

A. Yes, that is correct.

Q. Now, over the course of the past seven years you have published many papers, presented abstracts of many professional meetings. As I read your curriculum vitae, none of your

publications has yet been on the subject of digoxin, and I take it it is possible that may be remedied in the near future?

A. Conceivable, although we really do not know at this point. The major emphasis has been on drug toxicity.

Q. Dr. Spielberg, I will not embarrass you further with a recital of your achievements. You have provided me with a copy of a curriculum vitae, and I ask if you recognize it as I have described it?

A. Yes, that is correct.

MR. LAMEK: May that be the next exhibit, please, Mr. Commissioner?

THE COMMISSIONER: What number? 215?

MR. LAMEK: We have had 215.

THE COMMISSIONER: We are having an arugment as to whether it is 215 or 216. It is 216, you are right, 216.

---EXHIBIT NO. 216: Curriculum Vitae of Dr. Stephen Paul Spielberg.

MR. LAMEK: Q. Dr. Spielberg, I take it that both in the course of your pharmacological and medical training and in your later

activities as a teacher and as a clinical pharmacologist, you became familiar with the drug digoxin?

A. Yes, that is true.

Q. Is it fair, however, to say that until the past year or so you had not devoted any particular attention to that drug?

A. With the exception that we deal with it commonly in terms of consults and problems and such, probably the major emphasis has been over the last year in terms of more indepth examination of the drug, yes.

Q. And when you came to Toronto in July of 1981, the matters with which we are concerned here were then recent, although no doubt anguished, history of the Hospital, were they not?

A. Yes, that is correct.

Q. The charges were then pending against Nurse Nelles and the start of the Preliminary Inquiry was some six months in the future as of the date of your arrival?

A. Right.

Q. Dr. Spielberg, can you tell us when and how you first began to make any particular investigation of this drug?

A. The major initiating events

were the end of the preliminary hearing, and subsequently, some concerns brought by members of the Research Institute, leading to a meeting of various people within the Research Institute, Pharmacology, Cardiology and such, to see if there was anything that we could contribute on a scientific basis to what had already gone on before. In other words, was there any contribution that clinical pharmacology could make to further understanding and further help elucidate what had gone on before.

This was pretty much -- I do not remember the exact timing. It was several weeks after the end of the preliminary hearings.

Q. So we are talking about the spring or early summer of 1982?

A. Yes, that is right.

Q. And as a result of that, did you undertake any sort of literature review to increase your knowledge about the levels of this drug that one might expect to see in blood and tissues, representing toxic or perhaps lethal effects?

A. Yes, we, as extensively as possible at that point and subsequently since the volume of literature has increased a great deal over

the last number of years, have tried to review what is known about digoxin, about its pharmacology, particularly with reference to children, with particular emphasis on issues related to matters of toxicity.

Q. Did you also seek to extend your knowledge about the pharmacokinetics of digoxin, that is to say, as I understand it, the movement and behaviour of the drug in the body?

A. Yes, exactly.

Q. And about its action in the body, its pharmacological activity?

A. Yes.

Q. And about its elimination from the body?

A. Yes.

Q. And about the interpretation of levels of digoxin found, among other things, in postmortem blood and tissues?

A. Yes, and certainly, as well, since we were constantly being asked about issues related to therapeutic levels of digoxin and how to interpret that in living patients as well, this is obviously an ongoing process as new information accrues.

Q. In the course of the past 18 months, Dr. Spielberg, have you engaged in any research studies or experiments with respect to digoxin?

A. There have been several things going on within the laboratory group as a whole, some related to issues in the way in which and the manner in which digoxin binds to tissues or in the ways in which that binding to tissues can be altered. My role has been at best peripheral in such studies.

Q. But you have, I take it, kept yourself aware of the work that has been going on there?

A. Certainly.

Q. Now, Dr. Spielberg, I have to tell you that the clinical pharmacologists have been held out to us here at this Commission as the experts who hold the key to the puzzles that we are grappling with.

The clinicians, that is to say, the cardiologists, the pathologists, the biochemists have all said that you are the chaps who can tell us what these various numbers mean and the numbers and the levels that have been measured in these

children.

Now, Dr. Spielberg, you are the first of the clinical pharmacologists who will address the digoxin levels in this Commission, and you are going to have to tell us whether our expectations have been realistically or unrealistically built up. I understand that of the 36 children with whom we are concerned, five of them have been reviewed in some detail by you?

A. Yes, that is correct.

Q. That is to say, Cook, Miller, Pacsai, Estrella and Inwood?

A. Yes.

Q. Now, I want to deal with each of those children with you, of course, and welcome your views on the children generally in the digoxin levels in particular. You are aware, I take it, Doctor, that digoxin levels have been measured in the blood and/or tissues of those five children and others?

A. Yes.

Q. And in particular, have been measured in some cases antemortem blood, in other cases postmortem blood?

A. Yes.

Q. In some cases fresh, that is to say, not fixed tissue taken at autopsy; in other cases, fixed tissues taken from autopsy, and also in tissues taken after exhumation of bodies. You are aware of the range of samples in which digoxin has been measured?

A. Yes, I am.

Q. And it has become clear to us, Dr. Spielberg, that the variety of samples presents many and varying problems of interpretation of the digoxin levels that have been measured in them, and I take it that you would agree with that as an observation?

A. Yes.

Q. Now, Dr. Spielberg, you have suggested to me that before you addressed particular levels in particular tissues of individual children, it might be helpful to all of us if you outline some of the basic pharmacological concepts that are involved and explain the nature of some of the problems and the difficulties as you see them in the interpretation of those levels and the consideration of the deaths of the children from a pharmacological point of view. I am going to sit down so that I am out of the way, and I would ask you

to do that, please.

I may, if something is unclear to me, ask you to explain it as you go along, but otherwise I am going to give you the floor for a little while.

I gather you would like to use the blackboard?

A. Yes, I think we ---

Q. Might it be more convenient if it faced out a little more?

A. Maybe we can ---

Q. Just angle it a little?

A. Yes, so obviously the Commissioner and the rest of the group can see it.

MR. LAMEK: Laurel and Hardy made a fortune doing this.

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DM/cr

MR. SCOTT: If you can get Mr. Lamek to sit down it is more than any of us can do.

THE COMMISSIONER: The only thing, I would like to say something about it, I don't know how important it is going to be, but you realize of course this will not be part of the record.

MR. LAMEK: Well, we do have copies of things that I gather Dr. Spielberg is going to put on the board, yes.

MR. SCOTT: I think we have, but didn't you want sheets of paper, Dr. Spielberg?

THE WITNESS: Yes, there are some graphs and a number of figures which we have Xeroxed. I am going to put those on the board as well so that we will be able to refer to hard copy as well as things on the board. At least part of the problem that we will have to deal with is, I hope, that in the preliminaries to all this we can at least be working with the same terminology and the same ideas, so that when we refer to them later on it will be a little bit easier to go back to.

MR. LAMEK: Mr. Commissioner, Dr. Spielberg has been good enough to provide me with copies for counsel of each of these documents, and I propose that we mark them at the end of whatever Dr. Spielberg has to say in this portion of his

evidence, all at one time, if we may.

THE COMMISSIONER: All right. I think everybody knows what the problem is. Yes, you go ahead, Doctor, please.

THE WITNESS: Okay. I think at the outset it is worth spending two or three moments just to try to put the entire problem that we are dealing with into context before going directly into the issues of digoxin pharmacokinetics and what digoxin as a drug is all about.

In the first place we are dealing with a reasonably old drug here. It has obviously been used in literally millions of patients with a great deal of efficacy, this includes children in cardiac failure. We know a great deal about it, but on the other hand like most drugs there is a tremendous amount we don't know about the compound.

To give you an example, aspirin was available in its current form for more than half a century before we had any idea how it worked and now that knowledge of mechanism of its action has totally changed our approach to this drug and how we use it.

Similarly with digoxin in the very recent past there has been a tremendous amount of new

information available on its kinetics; on its toxicity, and such new data sometimes forces us to re-examine old data and to re-examine some of our own old concepts about the drug and this is not bad, this is basically the basis of scientific progress. We have to accept that certain old concepts will be changed with time and will have to be modified based on new data.

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The second thing that we are facing is that unfortunately practically all the drugs that we commonly use in paediatrics, the kinetics of digoxin are probably the most complicated.

Now, for many compounds there is a reasonably simple relationship between the level of a drug found in blood; the level found in an active site in the body, perhaps a receptor we will call it, I will draw some pictures of what receptors might be, and that there is a reasonably straightforward relationship between the blood level of a drug and either the way the drug acts; the reason that we are using the drug; or its toxicity.

Well for digoxin sadly this is not as simple a case. It is tremendously complex. I hope in the next little while not to confuse the proceedings with the complexity, but the reality of

4 it is that we must deal with some of the complexities because to either trivialize or ignore it can lead to tremendous risk of misinterpreting numbers as we arrive at those numbers.

So our task then initially, as Mr. Lamek suggested, will be to review some general aspects of the pharmacokinetics of the drug; how it's handled in the body; emphasizing really the key areas that we are going to need to look at the specific patients. I don't want to review everything that Dr. Mirkin has already told you, but we are going to have to review some basic pharmacokinetic issues so we are at least all speaking the same language.

There are several points I think we are going to have to recognize as we go through the general exercise.

The first is that we are dealing with available data in only a few of the patients that we are involved in and the events that occurred on the cardiology wards. Many of these samples were obtained under less than optimal scientific circumstances. This is through no one's fault; obtaining clinical levels on patients and applying assays that are standardly used for clinical therapeutic drug monitoring, when we are asking more complex

questions than that is tremenously difficult. The reality of it is that many of the samples that we are going to have to deal with and try to arrive at answers were obtained under less than optimal circumstances.

The second point is that with digoxin, as with most drugs, there is tremendous inter-individual variability, vast differences. For example, in living patients and levels both in blood and in tissues, and we cannot ignore that variability because that variability is tremendously important in interpreting the levels of the results that we see in one specific child.

Probably the hardest thing we are going to have to deal with and it is as hard for us as pharmacologists who wish answers as it is for the Commission, is that there may be multiple different ways to arrive at the same blood level, be that a high or a low blood level. What we are going to have to do is examine each individual patient considering them initially as unique patients which indeed they may well be, explore a series of hypotheses as to how a blood level can be achieved; present to you the data for and against each hypothesis; initially assuming that the levels are correct and

valid, and then consider whether or not there are artefacts which we also have to take into consideration in interpreting the level. Because it may well be that we are dealing with uniformity here. In other words, a group of children who all arrived at their blood level in the same manner, but scientifically we have to at least explore the possibility that there is not a homogeneous group. We have to look at various different alternate hypothesis and try as best as possible to ascertain how confident we are of data and how confident we are of the interpretation of the data.

Our goal then is basically the goal of the Commission, which is to understand what happened to the infants on the cardiology service, and what relationship that has to digoxin levels. From my point of view that goal has to be viewed in the context of trying to gain the information for the parents of the children, who not only had to cope with the loss of a child but also with the anguish of all the subsequent events; as well as the anguish which is at least in part shared by all of us, the nurses, the doctors at the Hospital, everybody who has tried so hard for so long to investigate these proceedings and the community at large.

Our real dilemma is that not knowing

is a horrible burden for all of us. It is frustrating, it is angering, and I hope that what we can do in the next little while is to at least define for the Commission what is known, what is unknown, the assumption and caveats we are putting behind all our data, because everything that I say and everything that other witnesses say about the data are going to be dependent on our scientific assumptions and our explicit statements of the caveats and problems associated with this data. I hope in the end that the information we provide will be useful to the Commission in arriving at some sort of conclusion as to what occurred.

Well having said that as an initiation. Digoxin: what can we say about its pharmacology, what can we say about what we know and what we don't know.

Is this going to work if I stand over here with the microphone?

MR. LAMEK: Why don't you take mine.

THE WITNESS: Now again I don't propose to go over everything that Dr. Mirkin has already gone through with you. Let us say for the moment that digoxin is one of the group of drugs loosely called digitalis, and we will ignore for the

8 moment the other digitalis preparations because clinically digoxin is the drug that we are going to be using and that is used in the patients of concern.

The two major indications for the use of the drug, because we have to say why we use it, are congestive heart failure, we will just abbreviate it and call it CHF, and that is the major reason that we are going to be using the drug in children.

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It is going to be to increase the ability of a failing heart to effectively pump blood to the rest of the body. This is its major indication.

There is another indication though that we will have to talk about which also applies to at least one of the children that we will be discussing and, that is, to treat abnormalities not now in the way in which the heart pumps but the electrical activity of the heart, disturbances of cardiac rhythm.

So that these are the two major indications that we have to deal with in the broadest sense. I am not going to go through the rest of what was already presented to the hearing by other witnesses with respect to that.

We do have to deal however with a few bits of basic pharmacology. In order for digoxin to work, it has to bind to things that we will call receptors. Now, what does that mean? Basically now if we look at a cell, the cell has a nucleus, be this a cardiac cell or a cell in the liver or wherever. This is its membrane. On the presence of this outer coating of the cell there are various different proteins which will interact with drugs. We will call these interacting proteins or binding protein receptors. There is a specific receptor by which

C.2

digoxin effects are mediated and we are going to have to at least have the term present because we will refer back to it. It is called a sodium potassium ATP ase. It is a very fancy term. Basically, digoxin will have to bind or stick in a specific way to this sodium potassium ATP ase in order for the effects of the drug to become manifest.

What does this long word mean? Basically the ATP ase is an enzyme that regulates the amount of sodium and potassium inside and outside of cells. What digoxin does is to inhibit this enzyme. This can change the relative balances of sodium and potassium across a cell and by mechanisms that are not completely defined lead to the entry of something else, calcium into the cell, and it is believed that a coupling mechanism between digoxin inhibiting this enzyme, altering sodium and potassium across the membrane and thereby causing calcium entry into cardiac cells, and there is a lot of black box in here that we don't understand fully, but the entry of calcium into the cells leads to the ability of the cell to act better, to pump harder, to be more efficient. That's the basic way in which digoxin works to improve contraction of the heart.

(2) There is another effect, or really

C.3

several effects though that we have to deal with. And some of those deal with effects on rhythm.

Now, you will excuse me, I draw rather badly, so, this is not going to look like a heart but we will do the best we can. It looks not at all like a heart. In any case, the points I think can be made.

The rhythm of the heart is complex and we are only going to focus on a few things. One is that there is some control of heart rate by something called the vagus nerve. This is a nerve that originates ultimately in the brain and increased firing of the vagus nerve tends to slow the rate of the heart, bradycardia, something that has been repeated.

MR. SCOTT: Doctor, is there any chance that you could straighten out the board just a little bit so that the Judge can see it. We must pay him some slight attention, even on Mondays.

THE WITNESS: Okay. It is difficult talking to an audience that is sort of in an L-shape.

MR. SCOTT: Don't bother talking to us, talk to him.

THE WITNESS: Okay, fine. All righty.

THE COMMISSIONER: Don't pay too much attention to what Mr. Scott says. I can follow it.

C.4

THE WITNESS: I have a dilemma, who do I listen to?

THE COMMISSIONER: So far I have been able to follow it.

THE WITNESS: Okay.

THE COMMISSIONER: I don't promise that I will give you ...

THE WITNESS: Well, we are going to try to go reasonably slowly because the concepts are important and we will have to repeat them with each individual child.

THE COMMISSIONER: The audience are not really smart.

THE WITNESS: Okay.

THE COMMISSIONER: Yes, all right.

THE WITNESS: Back to our heart. The vegus nerve is one way in which heart rate is controlled. An increased firing of the vegus nerve will tend to slow the heart. Now, there is something called the sinoatrial node, which we will call the SA node, and something else called the atrial ventricular node, which is between the small chambers of the heart, the atrium, and the ventricle, which we will call the A-V node.

Now, when you give somebody digoxin in

reasonably therapeutic concentrations, okay, several things happen. If you look at an electrocardiogram, and again, I am not an electrophysiologist and I don't want to put up the cardiogram, we will just talk about what happens, the rate of conduction from the atrium to the ventricle is slowed. This is mediated in part by increased discharge of the vegus nerve which digoxin can produce by central mechanisms acting in the brain, but it also is a direct effect of digoxin on the conducting system of the heart. If you completely block the vagus nerve digoxin will still cause a lengthening of the time that it takes from electrical impulse to get from here to here.

Now, we use that therapeutically under certain circumstances and one of the babies that we will be talking about had a rhythm disturbance originating up here. The rate was too fast up here and what happens is if the rate in the atrium becomes extremely rapid and the ventricle fouls that rate, the ventricle is beating so fast that it can't work efficiently and under those circumstances it is working at a rate that does not allow it to adequately pump blood. If we give digoxin it can slow the rate of conduction from the atrium to the ventricle, the parts of the heart that deliver the blood to the

C.6

rest of the body and we can take advantage of that to slow the response rate of the ventricle to the rapid rate up here, and this happened in one of the babies.

What that does then is allow the ventricle to work more efficiently and again pump blood better.

Now, as one keeps going up in dose with digoxin, and we will talk about toxicity in a moment, but as the dose keeps going up eventually you get overt slowing of the heart or, again, bradycardia, and you can ultimately end up with complete atrial ventricular dissociation, or what we call A-V block is the easiest way to call it.

So that now the ventricle has lost the regulatory pattern from up here altogether and is beating at its own rate. That can occur from a wide variety of pathophysiologic conditions as well as from dig., as we will see in a moment, but that is what ultimately will happen. We will talk about the other rate disturbances with digoxin in a moment.

I think that gives you an idea of the therapeutic use; No. 1, specifically acting on receptors in the heart to increase the force of contraction in heart failure and, two, the second

C.7

therapeutic reason to act as blocking conduction in situations where there is too rapid a rate up here and what we want to do is slow the ventricular rate to increase the performance of the heart.

Now,we have to turn from that very brief introduction then to how digoxin works and why we use digoxin to its kinetics. One of the figures which I will provide you I will reproduce up here, there is already hard copy of this.

Now, what we are going to do is look at an intravenous situation, and we are going to stick to intravenous administration of digoxin for the rest of this discussion of kinetics.

What we have plotted on this axis is the concentration of digoxin. Now, this is plotted in a logarithmic plot. What do I mean by that? Simply, that the intervals, equal intervals, are going to be tenfold instead of one; for example, if this is 1, 10, 100, okay, so that equal intervals are actually going up very, very rapidly, okay.

Now, I'm going to leave the axes off because I don't want to misinterpret from the graph what the actual levels will be, we will calculate those in a moment.

What happens when digoxin is injected

C.8

intravenously is that it initially enters serum, okay, or blood plasma. At that time there is an extremely high concentration of digoxin in serum. So that if one, for example, measured serum at the time of injection, you get very, very high numbers.

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Within a matter of minutes, and we do not really know how many minutes because the experiment cannot be done, although accidentally we often end up with numbers like this, but within a matter of several minutes, the level rapidly decreases and enters what we will have to call and is labelled on here as a central compartment or a central volume of distribution and we are going to have to define all these things and we will go back to it. From this central compartment, it then distributes extremely widely to the rest of the body with a dramatic drop in blood levels still from here to here. This process I have labelled on here the alpha phase. What alpha phase means is that the drug is not leaving the body, but it is distributing within the body presumably, at least in part, by binding to all the various different sites, in heart, in skeletal muscle, in liver, in kidney, really throughout the body. Any place there is an ATP ase, digoxin theoretically can bind.

This phase from here to here we are talking about now half hour to hour intervals. Most of the literature suggests that the time it takes for digoxin to distribute from here, from its cental volume after it leaves serum initially, down to its

final concentration or what we will call a steady state concentration, that this declines with a half life of about 30 minutes. The range in the literature is 20 to 60 minutes. That means in each half life, half the drug which is in the central compartment will disappear from that compartment and enter tissue.

In a practical sense, we usually talk about five half lives for the drug to be reasonably fully distributed. So to assure ourselves that we are beyond this alpha phase of distribution, if we are obtaining a blood level, we have to talk about five half lives or at least two and a half hours after the drug is administered.

Now, in a practical sense when we are on the wards and advising the staff and physicians how to use blood levels in monitoring their patients, we generally recommend that they do not obtain a blood level anywhere within the first, say, four to six hours after a dose to assure that with the variability that exists from patient to patient, that in fact the distribution is complete. Once the drug, then, is distributed through the body, it is then very slowly excreted from the body, and that is what this line represents.

Here we are now talking hours to days

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for the body to eliminate a dose of digoxin. The figures I have here give half lives anywhere from 20 to 80 hours. It is highly variable. It is age dependent. There may be genetic differences, both in renal elimination or kidney elimination of the drug as well as the rate at which the liver can metabolize the drug. There is probably a good deal of variation in metabolic changes of the drug from the drug into metabolites which occur. This is very slow. We call this the beta phase, and this represents elimination from the body.

Well, what kinds of numbers are we talking about? This is what we have to deal with initially. Can we put some sort of numbers on these kinds of phenomena? What I would like to suggest initially is a theoretical child given a therapeutic dose of digoxin. We will say that the amount of digoxin is 20 micrograms per kilogram of body weight intravenously. This would be a fraction of an initial loading dose, assuming that the child were not taking digoxin and we wished reasonably rapidly to achieve a therapeutic concentration. So that this is a dose that one would reasonably commonly see being used on the wards as an intravenous dose.

How high a level can one achieve from

20 micrograms per kilogram. Well, when the drug enters the serum--again this is the very rapid seconds to minutes issue here. When the drug first enters serum so that if you, for instance, had an IV in one vein and drew blood either as the IV was running or immediately thereafter, it sounds like it never happens in clinical practice, unfortunately, sometimes it does, particularly with drugs that take a while to run in the IV line, a house officer will draw a blood sample while the drug is still running into the other arm, we can get extremely high concentrations.

How high? Well, the amount of serum in the body is about 0.04 litres per kilogram. This is 40 millilitres of serum per kilogram of body weight, which means now that the 20 micrograms is going to have to dissolve in 40 millilitres.

This gives us a concentration of approximately 500 -- well, let us do it this way -- micrograms per litre, or the usual way we express it is 500 nanograms per ml. That is the maximum achievable concentration, assuming a quick bolus and an immediate blood level being taken.

Again, the exact time course of this decrease we really do not know. It has not been scientifically ascertained.

Now we get down to the central volume of distribution. It is a hard concept, volume of distribution. Do not think of it as an anatomical space. It is not, you know, blood plus a little bit of body water or something like that. It is an artificial construct.

The way we arrive at it is simply by giving a dose and then measuring the level and asking at time X when we measure the level, how much water would the drug have to be dissolved in to get the serum concentration which we have. The central volume of distribution of digoxin varies from .6 to 1 litre per kilogram. So that as the drug enters its central volume of distribution, the 20 micrograms per kilogram administered then would come up somewhere between dividing one into 20, 20 nanograms per ml or a maximum, if it only ends up dissolved in a half of a litre in a specific child, 40 nanograms per ml.

Now, it is not at all infrequent in clinical practice ---

THE COMMISSIONER: Before you go any farther, Doctor, at what point is that on the graph?

THE WITNESS: Now, this would be here. After the drug now has left serum and entered the central volume of distribution, and from here, now,

to the final, we are talking about a timeframe of at least two and a half hours gradually, slowly coming down from this maximum to the minimum, which we will list in a moment.

So,seconds to minutes after injection, this has now gone down to this. This is a very rapid
6
fall, obviously, from 500 down to 20 or 40.

THE COMMISSIONER: And that is in what period?

THE WITNESS: And it is happening now in a matter of seconds to minutes. How many minutes, we really just do not know. We really just do not know. Presumably it is a reasonably rapid phenomena.

So we are going 500, 20 to 40. This is seconds to minutes. It is probably several minutes anyway, but we do not know exactly, confounded by the fact that if the drug is still being administered, if it is still present in an IV line, it can still be that high.

Now we are decreasing with a half life of 30 minutes. So 20 is going to 10 in 30 minutes, then the next 30 minutes it is going to 5, and the next 30 minutes on down to its final volume of distribution.

Now, when the drug now begins binding

throughout the body, we are talking about a concept that does not make any sense: 15 litres per kilogram. Well, a kilogram of water only weighs a litre. So how can you have 15 litres per kilogram? What it means is that the drug is binding extensively in tissues throughout the body so that the amount we are sampling in serum is tiny compared to the amount that is bound and distributed throughout the body, and we will get back to that concept.

7 At that point, at full distribution and we go from volumes of anywhere from 5 to 20, it is highly variable, it is age dependent, it is dependent on the clinical status of the patient, we are now down to levels of 1 to 4 nanograms per ml, much closer to the therapeutic level that one wishes to achieve.

THE COMMISSIONER: Where is that now?

THE WITNESS: That would be here. Then at that point, the drug is going to be -- assuming the child gets no further digoxin, of course, the drug will then be slowly excreted over time with a half life of about 40 hours, shall we say, as an average, or maybe a little bit less. It is again age dependent.

THE COMMISSIONER: That point that you

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have just used is roughly how many hours after the injection?

THE WITNESS: This would be roughly two and a half to four hours after an injection.

So to summarize, immediately 500 nanograms per ml, very rapidly distributing to a central volume of 20 to 40 nanograms per ml, then slowly declining from 20 to 40 down to 1 to 4 over a period of two and a half to four hours is probably a fair estimate, and then declining down to zero eventually with a half life in the range of 20 to 80 hours, a very broad, very variable range.

THE COMMISSIONER: You have been using this half life. We have had this half life before, but you use it in quite a different way than I had understood it. You are talking about half lives all the way down the ---

THE WITNESS: They are different half lives.

THE COMMISSIONER: We have heard of a half life of drugs generally, and a half life of digoxin, but when you use a half life you use a half life for a particular period.

THE WITNESS: One has to with digoxin. What we are really looking at is how long it takes for

9 different processes to occur. See for most drugs we do not have to worry about this alpha phase and beta phase and everything, and then we are simply talking about excretion half lives. When most people talk about half life in a general sense, they are talking about this elimination phase from the body, how long it takes a drug, once in the body, to leave the body.

With digoxin, because it has this strange behaviour of starting out at one concentration and then declining to another, we talk about half life of going from here to here, and then another half life of going from here to here. This is its alpha half life or distribution half life; this is its beta half life or elimination half life.

Basically, the concept is being applied in order to try and understand how the drug actually ends up being handled in the body. Unfortunately, for digoxin we have this confusing pattern.

THE COMMISSIONER: Just so I will have it straight, what you are talking about in distribution is the half life from the very beginning, from the injection?

THE WITNESS: The distribution half life probably includes this because this is very

short, but it is typically the half life from the central volume down to here. But you know, two and a half hours is much, much greater than seconds to minutes, so that this is usually missed in calculations.

THE COMMISSIONER: And you say it is 20 to 80 hours in excretion?

THE WITNESS: 20 to 80 hours for excretion, half life, this is the beta phase, and about 30 minutes, 20 to 60 minutes for this phase to occur, the half life. Again, for it to be complete is five half lives.

MR. SCOTT: Mr. Commissioner, I am not understanding. I wonder if I could just ask ---

THE COMMISSIONER: Yes, certainly.

MR. SCOTT: -- because I am getting the impression from what the Doctor is saying that on his example it would be excreted completely within 20 to 80 hours; am I right about that?

THE WITNESS: That would be the half life, so you would have to wait five half lives for it to be completely gone.

MR. SCOTT: Which is 20 to 80 times 5?

THE WITNESS: Times 5, right. So five days to perhaps 20 days, if the half life is very long.

THE COMMISSIONER: Why do they call it

a half life if it takes five of them to make a whole?

THE WITNESS: Okay, it is basically based on a logarithmic concept. In general sense, the body for drugs like digoxin, anyway, we will leave it like that, these are dependent not on total fixed amount per unit time but on per cent per unit time. For example, in one half life we go from 20 to 10. In the second half life we do not excrete 10, we go from 10 to 5, and in the third we go from 5 to 2.5, and in the fourth we go from 2.5 to 1.25. In one half life you go down half.

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THE COMMISSIONER: Assuming that you had a concentration of 4 at that time it would be down to 2?

THE WITNESS: Right, exactly, exactly. So that wherever you are at is dependent not on the level but on the percentage decrease, how long it takes to get half of whatever process you are talking about accomplished, going from this down to half of this is one half life; going from here down to one half of this is one half life.

MR. SCOTT: Professor Spielberg, you have to remember for me that I am typical of your audience here, the Commissioner is different, but we took literature and history in school, and if we had to take science we took botany.

THE WITNESS: Well, this applies to plant life too, the doubling time of cells is the same thing.

MR. SCOTT: You have to be straightforward and simple about it because I don't understand this.

THE WITNESS: Maybe we can use botany for an example.

THE COMMISSIONER: No, that's fine.

THE WITNESS: No, no, in a serious

E.2

sense just to give you an example.

MR. OLAH: Mr. Commissioner, I have one questions.

THE COMMISSIONER: Yes, Mr. Olah?

MR. OLAH: The doctor did not indicate what the point between the alpha and the beta base is, is that steady state, Doctor?

THE WITNESS: We will have to define it more carefully, okay, and we will in a moment. The concentrations that we achieve after the alpha phase of distribution has occurred are going to be defined as more or less steady state, recognizing that the level of change during this period of time is so slow that if one measures a blood level at 10 hours, or at 5 hours it is not going to be very much different. The steady state is a relative term because this is declining but it is declining at such a slow rate that for practical purposes we are not into the problems we are dealing with here, where minute to minute the level is dramatically changing.

Let me just try half life in the opposite direction, it might help.

THE COMMISSIONER: I wonder if I could help you a little bit, Doctor. I don't intend to go into competition with you at any time. All I really

E.3

want to know is what your final answer is on these things.

THE WITNESS: Right.

THE COMMISSIONER: I think I now have what you have told us that it is going to take so many hours to get to one point and so many hours to get to another point, and I am quite happy to leave it at that, now some other counsel may not, they may be smarter than I am and prepared to prove you are wrong, but I am not.

MR. TOBIAS: Mr. Commissioner?

THE COMMISSIONER: Yes, Mr. Tobias.

MR. TOBIAS: If I could just ask one question on that very point. Did I understand your evidence to be, Doctor, that to get to the point where the drug starts to be eliminated it is about two and a half to four hours from the time of the injection?

THE WITNESS: In a general sense that is probably an acceptable way of looking at it, but there is some elimination going on even during the distributive phase, but it is very small compared to the distribution.

MR. TOBIAS: To get to the beta phase you say it is about two and a half to four hours?

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THE WITNESS: It would be two and a half to four hours, exactly. Okay, we will come back to it obviously and maybe when we are looking at specific examples it will indeed be of help.

THE COMMISSIONER: I am sorry, I was saying I am now a little confused. Two and a half hours, is that the half life?

THE WITNESS: That is the alpha half life.

THE COMMISSIONER: The alpha half life, so really it is ---

THE WITNESS: The distribution half life.

THE COMMISSIONER: To make sure it is all distributed it would take five times that?

THE WITNESS: Yes.

THE COMMISSIONER: So in the same way the 20 to 80 hours to make sure it is all distributed?

THE WITNESS: Right.

THE COMMISSIONER: But one half distributed at the end of the two and a half hours?

THE WITNESS: No, no, 30 minutes, the alpha half life is about 30 minutes.

THE COMMISSIONER: Oh, I see, I beg your pardon.

THE WITNESS: The alpha half life is

E.5

about 30 minutes, so this process of distribution is over in about two and a half to four hours.

THE COMMISSIONER: Yes, quite right. The half life on the excretion is 20 to 80 and you have to multiply that by 5 to get it all?

THE WITNESS: By 5 to get it all out of the body, right.

Now I realize we are going to have to struggle with this in a couple of different contexts, and two to four come up again,so hopefully as we go along we will be able to make it more apparent and more clear, and if necessary we will use the botantical examples because they are simple in a sense.

Let me just make the points that we need to make from this graph and from the kinetics.

In clinical practice when one is using blood levels to determine where the patient is at with respect to digoxin, we have to be tremendously cautious not to draw blood levels during this period of time because they can be very, very misleading. Because the first point to be made is that although for a matter of a very brief period of time you achieve levels even this high, and for a reasonably long period of time you achieve levels this high, there is no toxicity associated with that. During this

E.6

distribution despite the fact you have extremely high levels, the babies don't exhibit toxicity, and adults don't either. In a moment we will get into why that may be the case. But in any case in order to interpret the blood levels we need to know two different variables; the amount of drug that was given and the time from the injection to the time at which the sample was taken, and that obviously puts a major quandary on a lot of things that we have to deal with later. Because under many circumstances we have neither the time nor the amount, all we have is the level, and then we are going to have to struggle with where we are at in this kind of complex situation and indeed it is going to be a bit of a struggle, it is going to be a bit of a struggle.

Now to give you an idea there is a second figure here. Mr. Lamek, the Figure 2 that we talked about, do you want to distribute that because it may again be helpful to people. This is just to give you an idea, this is in one particular study in premature infants and it applies to somewhat older infants as well, but just to give you an idea. You also have copies of the original manuscripts so far.

The point to be made here again is some of the time dependents. Now in this particular

E.7

study they didn't look very, very early. The first blood sample obtained was an hour after the dose had been administered intravenously, so we are probably somewhere out in here, okay, in this portion of the curve, we have already begun declining from here. As you can see the mean blood level in those babies was about 10 an hour after the injection, but with a lot of variability, it ranged from 6 to 15 and this was only in a very few numbers of babies in fact. You can see that it took a very, very long period of time in these babies for it to come down to a reasonably constant level, even at 3 hours the mean was 5 and one of the babies had a level of 9. So the point again being that the process we are looking at is very strongly time dependent and that there is a significant amount of variability from one infant to another infant.

THE COMMISSIONER: Doctor, are these nanograms per millilitre?

THE WITNESS: They are in nanograms per millilitre, that is correct.

Now, Figure 3 tries to address the question of back extrapolating. What we have done here is to ask really the opposite question to what we

E.8

have looked at now. That is, if we have a specific blood level how much drug would have had to have been given to achieve that blood level, using these sorts of time-dependent phenomena.

THE COMMISSIONER: You have to know

(2) of course, you have to know the time.

THE WITNESS: Right. What I have done, this assumes a 4-kilogram child, that is important in the calculations, which is not a bad estimate of many of the children that we were dealing with, many of them were in that general weight category. What I am doing here is looking at acute, central and steady state. If we look at the graph the acute would be the seconds to minutes phenomena, or if circulation stopped at the time the drug was given; the central volume of distribution down here; and a steady state concentration which would be somewhere out in this range, and ask then how much drug would have to be given at each of these time intervals to produce a level of 100?

Well, if the drug was given at the time circulation stopped, or were being run in intravenously at the time someone drew a blood sample, again very, very short time interval, seconds to minutes, the amount required to produce a level of 100 would be

E.9

about 0.016 milligrams, this is calculating based on the volumes of distribution and a 4 kilogram child; that is 16 micrograms, which if you want to translate it into vials of digoxin is a fraction of 1 paediatric vial, it is a very, very small amount of digoxin, it is about one-third of one paediatric vial.

Now, let's say that you obtained a level that high and we are really over here now at the central volume of distribution. The drug now has left serum and is distributed in the central compartment, say 30 minutes after a dose or less, and with variability, then how much digoxin would have to be given to achieve 100 nanograms per ml. For a 4 kilogram child it comes out 0.4 milligrams, or 400 micrograms, this is less than one adult vial of digoxin which contains 0.5 milligrams, so it is about three-quarters or four-fifths rather, shall we say, of an adult vial or eight paediatric vials.

If we get down now to the steady state and we assume a steady state volume of distribution, which means that all this distribution has occurred now and we are way out here, how much digoxin would have to be given to achieve a level of 100 at the steady state which comes out about 6 milligrams, which is 12 adult vials and 120 paediatric vials.

E.10

Now, the point to be made is that because of the dramatic time dependency that we are dealing with here you can get drastically different levels of digoxin that would have to be administered to produce a specific blood level, and this is one of the major scientific quandaries that we have to struggle with as we work through each of the cases in a moment; is there any other way that we can provide corroboration of estimates of how much would have had to be given; when it would have had to be given; given that we are dealing with the situation that is tremendously time dependent, and also tremendously variable from one patient to the next patient. Okay. I don't have any figures to write for the moment, perhaps I will sit down for a moment.

THE COMMISSIONER: Yes, by all means.

THE WITNESS: Now, where does the digoxin go during this alpha phase? Well it goes into tissue and it goes into a variety of different tissues. It depends who you read in the literature in terms of the concentrations achieved in different organs, and this varies depending on autopsy techniques; it varies depending on whether it is a group of little children, old adults on digoxin, or middle aged adults, there are a lot of differences. In a general sense among

E.11

the highest concentrations one sees in the body after the drug now has distributed into tissues is in the heart. Even within the heart there are differences in different places in the heart. In a general sense there is more in ventricular muscle, the large pumping chambers on the bottom of the heart than there is in the atrium, the upper chambers of the heart. There are suggestions in the literature that there even may be differences in distribution within those chambers, for example, in papillary muscle, the little muscles that regulate the way the valve leaflets open and close, there may be very, very high concentrations.

Other organs also have a lot of digoxin in them. Kidney has a great deal, generally said to be somewhat more than liver, somewhat more than skeletal muscle; and brain also has some digoxin in it. Probably most organs really do have some. In fact even skin can have significant concentrations of digoxin.

Now with respect to the amount, or the percentage of digoxin in the body in different tissues, it is dependent not only on the concentration but on the weight of the organ. For instance, you could have a little tiny organ with a tremendous concentration of digoxin,but compared to the rest of the body it would

E.12

be a reasonably small amount and that has to be taken into consideration. That is going to vary with age because organ sizes vary dramatically with age. Liver is a different proportion of body weight in an infant than it is in an adult; brain is; heart is a different proportion.

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So, one has to be a little cautious in extrapolating data, particularly from adult autopsy information to the pediatric age group. Organ sizes can have a significant influence and furthermore nutritional status may as well. For example, if a baby is particularly malnourished as a result of disease state, he has been chronically ill and wasted, he may have much less subcutaneous fat, and there is some digoxin in fat and, similarly, if his protein intake has been bad during time, his muscle mass may be decreased so that the digoxin may have to, if you will, use the expression seek other places to go because there isn't as much muscle mass available for binding. And that can in fact influence kinetics somewhat.

Similarly, an infant with congestive heart disease, his heart is bigger. So that the total amount of digoxin might be influenced not only by the binding of the digoxin to his heart but also by the very fact that the infant has congestive heart failure.

Now, a major issue that we are going to have to deal with is variability. In the next figure, which is the fourth one, the relationship between serum and tissue concentrations, because this

is the next thing we have to get into, can we predict from serum concentrations what's going on in tissue or vice versa.

The first point to be made is that the relationship between serum concentrations and tissue concentrations is age dependent. There are data, for example, suggesting that in small children there is relatively more digoxin bound to, for example, red blood cells or more important in the situation heart muscle, than there is in the situation of older patients. Why this is isn't entirely clear. The suggestion is that per unit of weight of organ there may actually be more receptors for digoxin in children than in adults. What this means toxicologically in terms of adverse reactions isn't so clear, we will talk about that in a moment.

The second point is that the receptors conceivably could be saturated. We don't know if that is the case, but it occurs with most drugs and it is scientifically reasonable that saturation may occur in some patients; in other words, if you looked at the binding sites as a sponge and surrounded by some water, which would be the serum, at some point that sponge just can't take up any more digoxin. Now, that has major consequences because if that

F3

happens the addition of a tiny amount of addition of digoxin to the water surrounding the sponge will cause a big increase in the concentration in the water but no change in the sponge itself. This happens for most of the drugs which we use therapeutically at some concentrations. We don't say that we have good data on this in terms of digoxin per se but it is something we have to keep in the back of our minds because some patients may saturate at a low level so that their tissue levels may actually be very low and their serum levels very high and other patients may have much more capacity to bind, in which case their tissue levels would be proportionately higher compared to a specific blood level.

Well, do we have evidence for variability in tissue to blood levles? Yes, we do. I presented here some numbers. This is in micrograms per gram of tissue weight. You can see that it is quite variable. I chose three studies; one an older one and two new studies. The major reason being that there is reasonable concordance between the studies despite the fact that they were done by very different techniques and very different circumstances is reasonable concordance here.

The basic point is that on the average

F4

the figure that I think most of us would quote is that there can be easily tenfold differences in the ratio of heart muscle to serum concentrations among different patients. It is particularly important that in the second study American Journal of Diseases of Childhood, and the subsequent study as well in Clinical Pharmacology in Therapeutics were done in living patients. What was done is that these children were on digoxin chronically, and they were going for cardiac surgery. The digoxin was held 24 hours prior to surgery, which means we are not dealing with alpha phase distribution, this is an optimal scientific type of study where we can't be dealing with alpha phase, we are pretty much at a steady state.

As the surgeon entered the right atrium, which is the surgical approach used for the procedures, a tiny piece of tissue was taken from the incision and a simultaneous blood sample obtained and even under these optimal circumstances where we don't have to worry about alpha phase and we don't have to worry about continued administration, there was still tenfold variability in children chronically digitalized with no evidence of toxicity, entirely stable children going to operation from one patient

F5

to another.

Now, that may sound very dramatic and outlandish, to a pharmacologist it is entirely expected.

Particularly in children almost every drug that we use exhibits tremendous inter-individual variation. We are not in the least surprised, say, using a drug like theophylline in asthma that we can have six or eight or ninefold differences in the doses required to produce a blood level in a specific child and the kinetics of theophylline are much simpler than the kinetics of digoxin.

THE COMMISSIONER: Will you tell us what these figures, what they represent?

THE WITNESS: Yes, that is micrograms of digoxin, I'm sorry I didn't include that.

THE COMMISSIONER: Which is which?

THE WITNESS: The 84 to 325 is micrograms of digoxin per gram of tissue -- no, I'm sorry, I'm sorry, forgive me, I'm sorry.

What the numbers are is the ratio of myocardial concentration divided by serum concentration. So, for example, 84 means that there is 84 times as much in heart as there is in serum, 325 means that there is 325 times as much in myocardium

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or heart muscle as there is in serum. It is a ratio.

THE COMMISSIONER: I'm sorry.

THE WITNESS: And it is the ratio that exhibits the variability.

THE COMMISSIONER: I don't understand. I'm not even close to understanding it.

THE WITNESS: I'm sorry.

THE COMMISSIONER: So, you will have to try again.

THE WITNESS: Okay, let me try again. I am sorry for the confusion, that is entirely my fault.

THE COMMISSIONER: No, it isn't, but the fact of the matter is that I don't understand.

THE WITNESS: Okay.

All right. Now, I have explained the experiment to you, basically, in terms of how it is done.

THE COMMISSIONER: Yes, yes.

THE WITNESS: And what is done in the laboratory then is, you measure the amount of digoxin in the heart. Let's say you get X micrograms per gram of tissue. You then measure the amount in serum simultaneously and assuming that blood is reasonably the density of water, which it is very close to, you

F7

can estimate from microlitres back into grams, that is the advantage of the metric system is that liquids are convertible to weights directly, you get a value in the serum.

The number 84, for example, would mean that the amount in tissue, which is X, the amount in serum would be X divided by 84. It will be 184th as much or, if you want to look at it in the opposite direction, there would be 84 times as much digoxin per unit weight in tissue as there was in serum. What we are trying to get at is, can we pick out a relationship, looking at a blood level, can we guestimate what the serum is going to be versus the myocardial level.

What this tells us is that 84 to 325 means that in that situation you could have, some hearts had 84 times as much as in serum, other hearts had 325 as much.

Now, in the other studies we are dealing with numbers that range from 34 times to 363 times or 2.4 times to 340 times. The point being that the ratio of tissue to serum is highly variable. There is always more in tissue than there is in serum. In fact, there may be 300 some odd times as much in tissue as in serum but that the ratio is so variable,

ten times, that it becomes extremely difficult in an isolated serum concentration to know what the concentration would be in the heart or, if you were given a number in the heart to estimate what the serum concentration would be, you can make a guess, but it is going to be an average guess with tenfold error and that's the issue that one has to be concerned with.

THE COMMISSIONER: What are these RAA, what does that stand for?

THE WITNESS: Okay, right atrial appendage.

THE COMMISSIONER: Oh, I see.

THE WITNESS: I'm sorry that I didn't define this, they were made up very quickly. So, that is living right atrial appendage compared to blood. I hope that is clear because it is a terribly important point and it is something that we are going to have to deal with again when we get back to the issues of how we can look at either a tissue level or a serum level and from either in isolation try to estimate what the other would be.

THE COMMISSIONER: These experiments took place where and when?

THE WITNESS: A variety of different places.

THE COMMISSIONER: And how many are involved, do you know?

THE WITNESS: Reasonably large numbers. I would honestly have to go back to the original papers. These are not my data, these are the references, and Mr. Lamek has the original reprints.

MR. SCOTT: We have provided the papers to Mr. Lamek and I think he is duplicating them, if he hasn't done so already.

THE COMMISSIONER: Well, no, I just wanted to have some sort of general idea. Post mortem I take it means...

THE WITNESS: That study was done post mortem.

THE COMMISSIONER: And was that 1, 2 or 20?

THE WITNESS: I honestly don't remember. I would rather have the paper so we can tell you accurately.

THE COMMISSIONER: Then, the living?

THE WITNESS: The living patients, two different studies.

THE COMMISSIONER: Well, one of the studies has 2.4 to 340 which is a great deal more ---

THE WITNESS: Even more of a range.

F10

THE COMMISSIONER: More than - well, it is more like 1500, isn't it?

THE WITNESS: Well, what that says is that - sure, there may have been an error in that particular patient. What it says to me is that there probably are indeed outlyers in the population who have even more of a range of variability. Again, this isn't surprising. As you begin to collect more and more patients your range, generally speaking, gets broader and broader and broader because you are going to see all of the manifest different variables interplaying on level in tissue versus level in serum that can cause big spreads in the population.

THE COMMISSIONER: All right.

THE WITNESS: To be conservative we will say tenfold in general, but there are patients in fact who will be even greater than ten-fold.

THE COMMISSIONER: What concerns me is that it's not even 100-fold.

THE WITNESS: It's vast.

THE COMMISSIONER: It is 150-fold.

THE WITNESS: It's vast, yes.

THE COMMISSIONER: Yes.

F11

THE WITNESS: It's vast, yes.

THE COMMISSIONER: What's this last one then S/NS?

THE WITNESS: Okay. Well, I didn't really want to get into that at the moment.

THE COMMISSIONER: Oh, I'm sorry.

THE WITNESS: What that is is more of an analytical issue, it is specific versus non-specific digoxin. In other words, HPLC cleaned up samples versus crude samples examined by immunoassay.

THE COMMISSIONER: Yes, all right.

THE WITNESS: Again to point out that there is a lot of variability, but that is not something I think we need to get into and I think you have already heard a great deal about analytical kinds of problems with specific and non-specific digoxin.

MR. LAMEK: Dr. Spielberg, may I interrupt you just for a moment.

THE WITNESS: Sure.

MR. LAMEK: Mr. Scott is quite right, Mr. Commissioner. Dr. Spielberg has provided me via his counsel with copies of a paper which I think contains the study which gave rise to the postmortem numbers on this document. There is also a paper which

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has already been marked as Exhibit 19, Mr. Commissioner, on myocardial as opposed to serum digoxin concentrations in infants and adults. Perhaps I can distribute the other paper now.

THE COMMISSIONER: Yes, all right. Well, we are getting into trouble with these. I think we had better give them exhibit numbers. What is the next exhibit number, 217, and we will call them 217-1, 217-2, 217-3 and 217-4.

THE WITNESS: Mr. Lamek, you have both those studies, correct, the American Journal of Diseases of Childhood and the Clinical Pharmacology in Therapeutics, the old one and the new one, 1975.

THE COMMISSIONER: So, this will be 218 then.

MR. LAMEK: 218 then, the article from Clinical Pharmacology in Therapeutics.

THE WITNESS: Yes, there are two of them. There is one 1975 and one 1980, yes.

MR. SCOTT: Mr. Commissioner, have you marked the graphs?

THE COMMISSIONER: Yes, that will be 217-1, -2, -3 and -4.

MR. SCOTT: All right. And I take it in the order in which they were presented?

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THE WITNESS: Well, mine all had numbers on them. Did yours not?

MR. SCOTT: No, no.

MR. LAMEK: All right, in the order in which they were presented.

MR. SCOTT: So, 217-1 is the logarithmic Description.

THE COMMISSIONER: That's right.

MR. SCOTT: 217-2 is Levels in Premies.

THE COMMISSIONER: Yes, that's right.

MR. SCOTT: And 217-3 is the Calculated Dose to Produce 100 Nanograms.

THE COMMISSIONER: That's right.

MR. SCOTT: And 217-4 is the Relationship Between Serum and Tissue, is that right?

THE COMMISSIONER: That's right.

MR. SCOTT: And 218 is the article.

---EXHIBIT NO. 217-1: Logarithmic Graph.

---EXHIBIT NO. 217-2: Document entitled "Levels in Premies".

---EXHIBIT NO. 217-3: Document entitled "Calculated Dose to Produce 100 Nanograms".

---EXHIBIT NO. 217-4: Document entitled "Relationship between Serum and Tissue.

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---EXHIBIT NO. 218: Article from Clinical Pharmacology in Therapeutics.

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THE COMMISSIONER: Yes, and that leaves us, you see, with the opportunity, if we have any more diagrams, we can just go back to 217.

MR. LAMEK: Mr. Commissioner, there is one other paper of which Dr. Spielberg has given me a copy. This also is from Clinical Pharmacology and Therapeutics, May 1983. I do not believe that is already marked as an exhibit and I do not have copies of that for other counsel at the moment, but I can get them made. May that be 219?

THE COMMISSIONER: 219.

--- EXHIBIT NO. 219: Article from Clinical Pharmacology and Therapeutics entitled "Determination of Myocardial and Serum Digoxin Concentrations in Children by Specific and Nonspecific Assay Methods."

THE COMMISSIONER: We have to somehow or other distinguish them. Now, the first one is Tissue and ---

THE WITNESS: One of them is 1975, one 1983.

MR. LAMEK: Exhibit 218, I believe, is 1975.

THE COMMISSIONER: 1975, it may well be but there is no identification on it.

MS. CRONK: The bottom left-hand side of the page, sir.

THE COMMISSIONER: The bottom left-hand side of what page?

MR. SCOTT: The only person that I can hear talking in this room is Mr. Lamek. He has a good voice. I cannot hear when these exchanges go on. I am getting old.

MS. CRONK: On Exhibit 218, Mr. Commissioner, on the bottom left-hand side of the page you will see a reference to 1975, and on Exhibit 219 on the bottom left-hand side of the page you will see a reference to 1982.

THE COMMISSIONER: Yes, good for you, 1975, and the same thing, 1982. All right.

MR. LAMEK: Mr. Commissioner, just for ---

THE COMMISSIONER: So this one will be 218 and this one will be 219.

MR. LAMEK: I think for cross reference purposes, too, we could identify the three studies that are listed on Exhibit 217-4, the first, the post mortem study is I believe now Exhibit 218.

THE COMMISSIONER: Just a moment. 217-4 ---

MR. LAMEK: Yes, under "Myocardium/Serum" the post mortem study is now Exhibit 218; Living, RAA, Right

G.3

Atrial Appendage, is Exhibit 19; and Living, RAA 1983, is Exhibit 219.

THE COMMISSIONER: I am sorry, I have got two 219's.

MR. LAMEK: No, Exhibit '19 is the second one, the middle one. We had already marked that some months ago, sir.

THE COMMISSIONER: All right. Living, RAA ---

MR. LAMEK: Living, RAA, the 1982 article is Exhibit 19; Living, RAA, the 1983 article is I believe 219, that by way of a concordance.

THE COMMISSIONER: The 1982 article is 219.

MR. LAMEK: Mr. Commissioner, perhaps I can do it again.

The lower half of Exhibit 217-4 under the heading "Myocardium/Serum", the post mortem is Exhibit 218; Living, RAA with the numbers 34 to 363 is Exhibit 19; and the next is Exhibit 219.

THE COMMISSIONER: Yes, all right.

MR. LAMEK: Mr. Commissioner, having thus so successfully interrupted Dr. Spielberg's train of thought, could we perhaps take the break at this point?

G.4

THE WITNESS: Can I suggest just one additional sentence, maybe, just to put some things on the board because it will end that section.

THE COMMISSIONER: Yes, all right.

THE WITNESS: It will just take two seconds really -- well, five seconds maybe.

What I wanted to do is just list for you some of the things that might be responsible for this type of variability, and we will just make a list and then we will talk about them later.

One we talked about, is age, genetic differences, saturation -- we can get back to any of these you want -- and then we have to talk about disease state. Diseases of different kinds may, and we are going to have to say may because here is an area that is very gray even compared to some of the other areas we are talking about, hypothetically, such issues as oxygen, how much oxygen is in blood, how much acid is in blood, the relative balances of ions, sodium, potassium, magnesium, calcium, all of these things may influence the way that binding occurs from digoxin to its receptor. Glucose may be terribly important because the receptor is energy dependent, and if it is deprived of its energy either because of no oxygen coming to it or because of no

G.5

sugar coming to it, the receptor can be altered and modified. Other drugs, and we will talk about some of them, drugs like Quinidine, an anti-arrhythmic drug, can displace digoxin from its binding so that suddenly the digoxin loses its binding and comes back into serum; renal failure, and we will talk about that later as well. Kidney disease can, by mechanisms we are not entirely sure of, cause a loss of distribution of digoxin. It comes off of the receptors, it appears, and back out into serum, and finally, tissue death. If we have dying tissue, it can release its digoxin and the patient as a whole does not have to be dead for certain different areas of tissue to be in the process of dying or in fact have died functionally. Finally, we can add as a hypothetical various types of infections. There are now some data accumulating which I think are still too speculative to talk about in a hard sense, but which suggests that a variety of different phenomena which occur during infection can change membranes and the change that occurs in the membrane changes the ATP ase. Whether or not that really affects digoxin binding is highly speculative, but I think there is going to be some interesting things going on with that.

This is just to give you an idea of

G.6

the huge number of variables which can alter or change binding, and I think we can stop at that.

THE COMMISSIONER: Thank you. We will take 20 minutes.

--- Short recess

--- Upon resuming:

THE COMMISSIONER: The new table being distributed will be No. 217-5.

--- EXHIBIT NO. 217-5: Document entitled "Total Body Digoxin".

THE COMMISSIONER: Now, Mr. Lamek, I do not know whether to call on you or Dr. Spielberg, but whichever it is.

MR. LAMEK: If you call on me, I will call on Dr. Spielberg.

THE COMMISSIONER: All right. Yes, Doctor, do you want to proceed?

THE WITNESS: All right. Well, what we have done so far is to try to deal with some of the issues of kinetics, the time dependency, the uptake into tissues and some of the variabilities which can exist between serum levels and tissue levels, and the difficulties of extrapolation.

Now, what we have to head into now is an area that is actually a bit newer pharmacologically,

G.7

and I will try to be as careful as I can where we have hard fact and where we are speculating so that you will know where things are at.

I think that it should have become apparent from our discussion up to now that in reality when you look at digoxin, very, very little of the digoxin at steady state is in serum compared to the amount in the body. What do I mean by very, very little? Well, in a general sense at steady state, less than a half of a per cent of the total body digoxin is in serum. That is important because we are sampling serum. We cannot normally sample different tissues or other compartments, but we are sampling serum in the hope that that will tell us something about what is going on in the rest of the body.

Now, with most drugs, and the reason that therapeutic drug monitoring, for example, works is that there is a clear-cut relationship between the amount in the serum and the amount in tissue. We have already said that with digoxin that may not be the case; there is much more variability, and furthermore, 99.5 per cent plus of the digoxin is out there in tissues in compartments which we cannot readily assess and which our blood levels may not directly reflect for several reasons.

G.8

Now, the consequences of that are several ---

THE COMMISSIONER: Before you go on with that, that 99.5 per cent I found interesting and I would like to see if that compares with -- 500 nanograms down to ---

THE WITNESS: You cannot compare total amounts.

THE COMMISSIONER: No, but you said 99.5 per cent and we have not heard that figure before. If you look at 217-1, I take it this is the concentration of -- 500 has to go somewhere, it goes into tissues and some of it is excreted at the same time?

THE WITNESS: Right, a very small amount.

THE COMMISSIONER: Where did you get your figure of 99.5 per cent?

THE WITNESS: Okay. Now, that is shown in the next figure. Now, what we have to take into consideration is the amount of serum in the body compared to the total weight of the body and the relative concentrations in serum at given different times.

Now, what I have shown in this figure,

G.9

and let us just look at the top line -- we'll get into what the rest of it means in a moment -- the top line, we will assume a 4 kilogram child with a volume of distribution of 15 litres per kilogram. That is the steady state kind of concentration. We are now talking about pre-distributive. That means that in a 4-kilogram child, the total amount of digoxin in his body would be 120 micrograms.

How do we get that figure? If I go through the calculation, maybe it will make it clear for you then.

His body weight is 4 kilograms. The volume of distribution of the drug is 15 litres per kilogram. That means that the drug is distributed as though it were distributed in 4 times 15 equals 60 litres.

Now, we are sampling serum, and our serum tells us there are 2 nanograms per ml out of that 60. Two nanograms per ml is 2 micrograms per litre. To get then the total amount of digoxin in the body, we multiply the concentration of our sampling site, which is serum, times the total apparent volume of distribution, 60 litres equals 120 micrograms. Does that follow?

THE COMMISSIONER: No.

G.10

THE WITNESS: You are not happy with it yet.

THE COMMISSIONER: Well, I am not sure that I have to be happy with it. I want to know where you are going before I want to know whether I understand it.

THE WITNESS: Now, the next point is that is the total amount in the body. What is the amount in serum? To know the amount in serum we have to know how much serum there is in the body, and we will assume about 40 millilitres per kilogram of body weight is serum, because that is the compartment that we are sampling.

What we are asking, then, is if there are 2 nanograms per ml in serum and 40 millilitres per kilogram of body weight, how much of the digoxin actually is present in serum? Now, to do that, we have to multiply, then, the volume in which it is dissolved times the concentration. What we come up with is about, in here, .32 micrograms total in serum, 2 nanograms per ml times 40 ml per kilogram times 4 kilograms body weight.

THE COMMISSIONER: Well, I would have thought if you wanted to find the amount of digoxin in the serum you would measure it.

G.11

THE WITNESS: We have the concentration but we want the total amount. To get from concentration to total amount, you multipy the concentration times the volume.

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THE COMMISSIONER: I see. All right.

THE WITNESS: That is exactly what we have done here. We multiplied the concentration times the volume of the body to get at the total amount from the body. Here, we have multiplied the concentration times the volume of the serum to get at the total amount of serum.

THE COMMISSIONER: Right.

THE WITNESS: Now, the point is, when you do the calculation, you end up with something like 3/10 of a per cent of the total body digoxin present in the serum. It is a very, very small amount; a very, very small per cent.

THE COMMISSIONER: At a steady state?

THE WITNESS: At the steady state.

Now, the reason I bring this up is not trivial and it is a major point and one, again, that more recent data has a major impact on our understanding of digoxin.

What we want to do in the left here is now say, no digoxin is going to be administered to the patient but what we are going to do is release some of the digoxin from tissue into serum and ask the following question:

H2

To go from blood level A, which is 2 nanograms per millilitre, to blood level B, which is 30 nanograms per ml, how much digoxin has to be lost from the tissues in order to do that?

Now, we are going up 15 times the blood level, okay, from 2 to 30, but the amount of digoxin that has to be released from tissue, because tissue has so very much more digoxin in it, is only about 4 per cent; actually, 3.7 in this calculation but these are rough calculations and have to be viewed as such. In other words, for a massive increase in serum concentration, we have to lose only a tiny portion of the amount bound to tissue.

To go up all the way to 100 nanograms per ml in serum, assuming that the amount in the body is unchanged - no excretion, for example; total renal shutdown, okay - now we have a situation where the digoxin, the amount in the body is going to stay the same but more is going to be present in our sampling site in the serum. To go from 30 to 100, we have to lose an additional approximately 10 per cent - up to 13 per cent of bound digoxin has to be lost.

Now, this is an important concept because of several things that have become apparent

H3

over the last while. One is the phenomenon that has already been presented to you several times; that is, post mortem serum digoxin levels can increase, sometimes threefold, sometimes twofold - highly variable. The point being that, under those circumstances, no new digoxin is being introduced into the patient. What is happening is that some of the digoxin that is in tissue, presumably is being redistributed into serum. In other words, there is a loss of digoxin from tissue into serum. A very tiny loss can produce a rather significant increase in blood level, and this is important because if you sample tissue, you would never see the small losses. We have just said there can be there can be tenfold variability in tissue concentrations among the different patients; you would never be able to detect analytically a 10 per cent or a 13 per cent change in bound digoxin compared to the variability which exists among different patients.

The second point is that we are now begining to learn that such loss of binding or redistribution of digoxin can occur in living patients. There is literature now - Mr. Lamek has a copy of the paper "Annals of Internal Medicine" in 1983 examining renal failure as an example of this.

H4 Digoxin is not administered to the patient - it is stopped. He has been on digoxin so he is fully digitalized and has large amounts in his body. The digoxin is stopped and, yet, the digoxin blood level continues to rise. So, indeed, without any exogenous administration of digoxin, the possibility exists, under certain pathophysiologic conditions - the published condition being renal failure - for reasons that we don't fully understand, digoxin levels can rise in the absence of administration of digoxin, and that is something that we are going to have to cope with, both in vivo and in vitro.

What it says is, because of the huge amounts of digoxin in the body, small losses from tissue, very small losses compared to the total amount in the body, lost from binding sites, because the binding sites are damaged,or dying,or because other things are displacing the digoxin from the binding sites, can cause digoxin to redistribute back into serum; it can occasionally occur in vivo, and we will talk probably in the context of specific patients,what evidence we have for and against each specific situation. We know it can occur in renal failure. We know it can occur with drugs, such as quinidine. We know that it can occur from tissue

H5

death, or necrosis of different tissue where no exogenous administration in a patient who has digoxin on board already can cause a rise in serum levels, and that is the basic point to be made from that, and it is something, again, that we will have to cope with, both for in vitro situations and in living patients where loss of binding integrity has now been demonstrated to cause increases in serum levels, and in order to interpret post mortem levels where it is already a reasonably well-established scientific phenomenon that loss of binding from this huge pool can have a major influence on the small pool in serum.

To draw an analogy, the amount in serum is basically like a thimble compared to a bathtub in the body; reasonably small waves can swamp that thimble and markedly increase its levels without any apparent change or scientifically detectable change in the tissue levels. It is something we will have to cope with when we deal with the specific patients, both pre mortem and post mortem levels.

THE COMMISSIONER: One thing that concerns me. You say, the loss from tissues can result in massive increases in the serum levels, but

H6

does it all have to go to the serum, the loss from the tissues?

THE WITNESS: Eventually, yes.

THE COMMISSIONER: Fine.

THE WITNESS: It doesn't have many other places to go. Basically, if you look at an organ, for example, okay, with blood flow occurring, the blood is going to leave arteries into small arterioles and then into capillary arteries bathing the various different cells. There is exchange that exists between the cells in life or, for that matter, in death, as they are dying, releasing various excretory products into the serum that is then collected on the other end into the vein .

THE COMMISSIONER: I am only concerned, really, with the answer to the question; not with the reasons why you are getting there, because that is something I am prepared to rely upon your expertise more than mine. I just don't quite understand why it must go from the tissue to the serum.

You say it must. You say, if you lose it from the tissue, it must go to the serum.

What happens when bodies decay?

THE WITNESS: This is post mortem, for example?

H7

THE COMMISSIONER: Post mortem, yes.

THE WITNESS: Now, the --

THE COMMISSIONER: Digoxin, surely would not go from the tissues; it would go into the air, would it not?

THE WITNESS: No. It is not volatile, okay. In a situation where the body would be buried, there might be a lot of, you know, movement within tissues themselves, but basically, under those circumstances, there is no circulating serum.

THE COMMISSIONER: At any rate, do I understand --

THE WITNESS: We do know, however, that, in a situation, for example, where a patient has died, okay, and now there is no new blood circulation, if we obtain a sample at the moment of death - if that were possible - and then several hours or days later, in fact, the concentration of serum has gone up, or in blood has gone up, and, again, our best hypothesis for this is redistribution into blood.

What we are dealing with when tissues die is digoxin is going to go into body water and that body water is then going to redistribute into serum. It really doesn't basically have too many other places to go.

H8

THE COMMISSIONER: What you are telling us is it does go into serum --

THE WITNESS: Yes.

THE COMMISSIONER: -- when it redistributes itself from the tissue?

THE WITNESS: This certainly would be the case in vivo. It is the case from immediate post mortem until autopsy. For buried tissue, it is a very different kind of phenomenon, and I don't think even we can comment on it because we are not sure what happens to it. Some of it is broken down by bacteria and fungi and such, but that is really a very different issue.

THE COMMISSIONER: You are assuming there is no excretion at all?

THE WITNESS: Yes.

THE COMMISSIONER: If there is any excretion, that is probably where it will go?

THE WITNESS: Yes.

THE COMMISSIONER: Fine.

In the ordinary course, that is what does happen, I take it? The digoxin goes from the serum to the tissues and then is excreted?

THE WITNESS: It comes back into serum; it can't be excreted from the tissues.

H9

THE COMMISSIONER: It can only be excreted from the serum?

THE WITNESS: Right. Blood is going to profuse the kidney or liver. So, in other words, for instance, if I have a molecule of digoxin sitting out in my skeletal muscle in my arm, the only way it is going to exit the body is by re-entering blood, being transported to either the kidney tubial or the glomerulus for filtering or pumping directly into urine; or, perhaps also, to be metabolized in the liver. Okay. It can't exit the body except by that type of physiology.

THE COMMISSIONER: Take the case of the heart, first of all --

THE WITNESS: Right.

THE COMMISSIONER: -- it goes back into serum and then from the serum it goes eventually to the kidneys --

THE WITNESS: Right.

THE COMMISSIONER: -- and then out?

THE WITNESS: Right. That would be the simplest view of it and reasonably close to the physiology of the situation. I think it is sort of best left at that - there is really no other mode of exit for it except by metabolism in the liver.

H10 Now, having said all that, we have to get to one of the major clinical issues. In other words, is there a good correlation between blood level and toxicity? This is a complicated issue and we have already brought up some of the complications. We have said that, because of the distribution phase, you can have extremely high concentrations with no toxicity whatsoever as the drug distributes in the body. We have also said there is a great deal of variability in the tissue-to-blood ratio and, if most of the toxicity is mediated at the level of tissue - which is what we believe it is - and the blood does not necessarily well reflect that, you would imagine that blood levels would not be all that helpful except as a rough guide to toxicity.

Now, I would like to, since it is said so much better here, try to provide you something, and I will provide the actual quotation from Goodman and Gilman, which is a standard pharmacology text, the 6th Edition, 1980, and it contains a lot of what obviously is outdated material because of the progress that has been made since. I think it states the situation very well.

First, let me list the manifestations of toxicity and then get into the correlation

H11 with level.

The standard things we talk about are nausea and vomiting from digoxin toxicity, a very non-specific kind of sign, obviously, since nausea and vomiting can originate from many different sources. It is thought that much of the nausea and vomiting may be mediated by digoxin effects in the brain in an area called the vomiting centre, if you will, chemoreceptive trigger zone, a fancy term for the vomiting centre. Some of it may also be mediated directly on the gut since diarrhea also can rarely result from digoxin toxicity.

Then we have a series of other somewhat less common events, which can occur with digoxin toxicity, and we will have to go through some of them.

Changes in the central nervous system, sometimes confusion. These are very high concentrations. Sometimes delirum. Very peculiar changes in vision, often, in adults, described as "things looked yellow". This was invoked in why Van Gogh painted the way he did - there are all sorts of stories of whether Van Gogh had been digoxin-poisoned. And I won't comment any further on that. It may colour the way you look at the world,

H12 shall we say - and no pun intended.

Clearly, another interesting one is gynecomastia - which means breast enlargement in men. Because digoxin is very similar to some of the steroid hormones that are present in the body, digoxin can cause breast engorgement. In fact, sometimes we see breast engorgement in children on digoxin. It is reasonably rare but it sometimes does happen and it is, at least, worth mentioning.

Clearly, the things we are concerned about are the effects on the heart. That is the major issue.

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And what kinds of toxicity occur with digoxin in the heart. We have already said that one of the effects of digoxin is on the Vagus nerve and on the rate of the heart. So that cardiac slowing, decreased heart rate may or may not be a sign of digoxin toxicity, but certainly a slowing of the heart is one of the manifestations of digoxin toxicity.

The next group are things that we will call dysrhythmias. Some people call them arrhythmias. Since 'A' means non I think probably dysrhythmia is a better term. And what they are are abnormal electrical patterns in the heart, abnormal rates. Some may originate at the level of the atrium and some may originate at the level of the ventricle.

To make a long story short, almost any type of arrhythmia can result from digoxin. It is said, and it frankly is difficult to get from the literature just how accurate the statement is, but it is generally said that atrial arrhythmias tend to be more common in children along with bradycardia, cardiac slowing. And in a general sense ventricular arrhythmias tend to be somewhat more common in adults. That is probably a generally okay statement with the following caveats that we have to add.

I.2

To quote Goodman and Gilman a little bit:

"It is important to realize that all disturbances of rhythm associated with high concentrations of digitalis in plasma or tissues are not necessarily manifestations of digitalis toxicity and that low concentrations of the drug in plasma do not preclude the possibility of drug induced arrhythmias.

The concentration measured in plasma can serve as only a crude guide to the likelihood of either efficacy or toxicity."

Now, the problem we are dealing with, really, is that we use digoxin in patients with diseased hearts and most of the abnormalities in rhythm which occur can be part of the disease state itself.

Again, to quote them:

"For example, an increase in the severity of heart failure often itself is the cause of atrial and ventricular arrhythmias. A patient who is simply getting sicker because of his heart

I.3

"disease is more likely to develop these kinds of arrhythmias."

So that it becomes extremely difficult to separate out the effects of the drug versus the heart disease that the patient has and probably the major confounder that we have to deal is the relationship between the patient's disease state and whether or not digoxin is playing a role in a rhythm disturbance.

What other things can alter the likelihood that these events will occur. A major one is hypoxia - decreased oxygen. For example, in adults who have had a heart attack they have an area of dead tissue sitting out in the ventricle. That by itself acts as a, quotation mark "irritable focus" end quotation marks for a ventricular arrhythmia. A very low concentration of digoxin might cause further arrhythmias in such a patient who already has an increased likelihood of an arrhythmia.

Similarly, big increases in oxygen will alter ATP ase function and can, again, predispose to arrhythmias, to which we now have to add hypoglycemia, decreased blood sugar, decreased serum potassium, a major thing. Most adults who get into trouble with digoxin from arrhythmias do so not

I.4

because their blood is excessively high but because their serum potassium is low because of the use of diuretics which waste potassium in the kidney.

So that probably although you would think the most common cause of digoxin toxicity is elevated digoxin levels, in clinical practice, at least in adults, the most common cause of digoxin toxicity is decreased potassium levels.

We also have to deal with calcium. Increased calcium levels can be associated with increased dig. toxicity and any plasma concentration, decreases in magnesium, and other ion. So, you see, there are a variety of things we have to cope with here and we have to look at each patients on their individual merits for all of these things.

Hypothyroidism, decreased thyroid. For reasons that we don't understand at all, many patients with hypothyroidism may get into cardiac problems, or heart problems, and they are very, very subject to digoxin toxicity at very low concentrations and we don't understand why, but that simply indeed occurs.

So, point to be made that you can have a patient in fact with a reasonably high level of digoxin with no manifestations of toxicity. You can

I.5

have a patient with very low concentrations of digoxin with manifestations of toxicity. How do we cope with this? Well, let's say we are dealing with a situation where we are asked to consult on a patient who has heart disease and we are asked to say, well, we just sent off a serum digoxin level and it came back 4. Okay, we normally talk about a therapeutic range and albeit that this is very broad and only guideline, these numbers are not emblazoned in stone, they are rough guidelines. In adults we go all the way from a half, maybe up to 2.5 nanograms per ml. Some people will extend that range up a little bit in patients, in children particularly, but in any case we use this as a rough guideline. So, let's say we get back a level of 4 nanograms per ml. and we receive a call about this and the patient is still alive. What do we need to know to interpret this level relative to whether or not it is a toxic level. We need to know certain things: first is the pharmacology. Time? When was the dose given, by what route was it given and when was the level drawn relative to the dose, because clearly if we are in that distributive phase, the 4 may be higher, it may be lower, we don't know because the concentrations we are talking about here are derived from steady state.

I.6

So, we really have to know whether this reflects a steady state or a pre-distributed state. The second thing we need to know is where the sample is obtained from. It sounds strange in a living patient but it can be important.

Not infrequently - well, probably the major cause that we find elevated digoxin levels are trivial issues of timing, the level is drawn too close to the dose. Probably 80 per cent of our consults are based on that.

Sampling error. In the ICU or in critically ill babies often it is very, very hard finding intravenous sites. Their veins have been used for multiple blood drawing and it is very difficult. Some babies have central lines, which means an IV catheter put into a large vein in the neck. That line is not infrequently used both to give medicines as well as to draw blood.

We have had now a number of experiences where somebody would draw the blood sample back from that central line and get extraordinarily high digoxin levels. We would call the floor and they would say, well, the patient is fine. What's going on? Well, what happens is, remember, we are giving digoxin in micrograms, we are measuring it in nanograms.

I.7

That is 1,000-fold difference. So that if even a tiny amount of digoxin sticks to the tubing or, for example, is still in the IV solution but settled out in the U portion of an IV tube as it hands down, it is very easy if we draw back on that line even several hours after the digoxin has been administered to pick up a tiny fraction of that dose and end up with extraordinary high numbers. So, we do have to know about sampling. It doesn't happen often but it happens enough that it is one of the questions that we routinely ask.

Now, let's say we know that it is a steady state level and we know that the sample was obtained correctly and we have a 4. The next thing we obviously need to know is the clinical status of the patient. What do we need to know about it? We need to know, is he manifesting any evidence whatsoever of digoxin toxicity. Well, let's say we are told that the patient hasn't been feeding very well that day and vomited his last feed. Okay, this might or might not be due to digoxin toxicity. Let's say he also has an arrhythmia, mild, easily manageable, but he has an arrhythmia. This might or might not be due to the fact that his digoxin level is 4. What is our response then? We have to look through

I.8

everything: all those factors we had on the board, oxygenization, potassium, calcium, all the variables that can have an impact on whether or not the patient is going to develop toxicity and then we have something we can do in a live patient. We can hold the digoxin. We can do an experiment. We stop the medicine and we watch as the level comes down, does the patient get better.

This is probably our single most useful tool in fact in clinical pharmacology when you are trying to assign a relationship between a series of symptoms and a drug or a drug level, removing the drug, decreasing the level is probably one of our better sensitive tools.

If we wanted to, and we wouldn't want to with digoxin, we could then increase the level again and see if the symptoms came back. A positive challenge. We wouldn't want to do that with as dangerous a drug as digoxin, but in the absence of clear evidence of improvement as the level came down, it would be extremely difficult for us to be sure that the elevated level was indeed the cause of the patient's nausea and vomiting or that the elevated level was the cause of his arrhythmia.

Now, what's the practical consequence

I.9

of this. If we have an elevated level which occurs in a baby in whom either the child dies or there is no opportunity to stop the digoxin to see what happens when the digoxin level indeed comes back down, we are missing a tremendously useful piece of diagnostic information and then we are going to have to cope with the far more difficult problem, and that is exactly what we are going to have to do with each of these children because in the situations for which we do have blood levels, we did not have the possibility in most of the children of dechallenging and examining what happens. That is probably one of our most useful tools. So, that has been removed from us. All we have are blood levels. We rarely have any information on time. We have problems to deal with in sampling.

THE COMMISSIONER: I'm sorry, we have all the information I think, do we not, on the time of delivery of injection?

THE WITNESS: We have time of last known dose but if another dose was given we don't know when it was given.

THE COMMISSIONER: No. But we do have the information on the time of delivery in each case and time of legitimate delivery.

I.10

THE WITNESS: The time of legitimate dosing, yes, that's correct, that's correct, yes.

THE COMMISSIONER: Yes.

THE WITNESS: But if an extra dose were given we lack that information.

THE COMMISSIONER: I'm afraid that's why we're here.

THE WITNESS: Exactly, exactly. So, this is where we are at at this point. What we are going to have to add on to all of the remaining discussion then are major issues in terms of how the samples are obtained and potential artefacts because when we get back these numbers our initial assumption is going to be and what we will try to do when we go through the specific patients is to assume that the numbers are correct and then see pharmacologically what sense we can make.

Recognizing that the numbers might not be correct, and what potential artefacts may have been introduced into each of the numbers, because we have to keep in mind the way in which samples are collected and what impact that may have on the numbers and in turn then what impact that may have on our interpretation.

Among the things that we will talk about,

T.11

we will talk about ---

We will talk about my beeper going off.

---Discussion off the record.

THE WITNESS: Sampling techniques we have to be very concerned about. This is going to apply particularly to postmortem sampling techniques and the way in which samples were obtained and we are going to try and do our very best to go through and look at the sampling techniques and to see what influence that may have on interpretation of our numbers, sites at which blood samples were obtained post mortem, the technique by which they were obtained post mortem.

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We are going to have to look at a variety of agonal events, by which I mean the kinds of things that occurred right around the time of death and the response during the resuscitation. Those are going to be very hard things to look at. They are areas where our data base is very small, some of it anecdotal, but it may have major impact on the ultimate numbers which result.

We are going to have to consider the effects of preservatives and of burial and of desiccation. We are going to have to look at possible changes, both chemical and bacterial and fungal on all of these phenomena.

The one caveat I at least have to say at the beginning, and it is a horrible frustration, I think, to us all, is that many of these variables we just cannot define and control for. We will do our best. I will try to point out those things that we do know something about, and where it is congecture, again, I will try my best to label it as congecture so that you will know where things stand.

To summarize where we are at up to this point, then, we have said that in terms of achieving a specific level, we have a series of potential hypotheses. We have the possibility of

J.2

excess administration of digoxin which we always have to keep in mind, and we have to look to see in each situation what type of administration and what kinds of volumes of administration and what sort of circumstances are more or less plausible. We have to look at pre-distribution, this kind of time-dependent phenomena and ask do we have evidence for or against a level resulting from problems related to timing. We have to look at the issue of variability from one patient to another because of the phenomenal overlaps in toxic and therapeutic ranges. We have to be very cautious in interpretation, but at the same time try to provide some interpretation for each patient. We have to look at the issues of de-distribution or loss from binding sites back into serum, which may play a role in some patients and may not play a role in other patients. Finally, we are going to have to look in each situation are there artefacts which are going to complicate our analysis and are going to make it more or less difficult for us to come to specific conclusions.

In doing so, again, I think our approach has to be looking at each individual patient on his own merit, what the hard data are, what the soft data are, what this tells us about the reasonable

J.3

probabilities of the various hypotheses before we then try to go back and group the patients together, with the one caveat that if indeed there is not homogeneity one cannot group. So we have to seek what evidence there is for and against homogeneity of at least the levels that we do indeed have at the moment.

I think we can stop there and then have Mr. Lamek proceed and we can discuss further.

MR. LAMEK: I have forgotten how.

THE COMMISSIONER: I take it we are now going to proceed to the children?

THE WITNESS: Unless there are things that we should review further.

THE COMMISSIONER: No, there is nothing we should review further, and we will proceed to the children right now.

MR. LAMEK: There may be a couple of things, Mr. Commissioner.

THE COMMISSIONER: All right.

MR. LAMEK: Q. Dr. Spielberg, thank you for that. It was helpful in defining some of the problems in interpretation.

As they say in minutes, a couple of matters arising out of it, if I may, though, please.

J.4

I was struck at the outset when you told us of the long history of use of digitalis preparations and the width and breadth of their use. You said digoxin has been used on millions of patients. Are you able to help us from your review of the literature approximately how many reported fatalities are there from digoxin intoxication in hospital settings?

A. I cannot give you a good number on that in honesty. To give you -- well, let me just check one potential source. You would obviously have to look, I think, very carefully at both patient population, ages and such of patients. One of the things that standardly -- they do not quote a number in here unfortunately. I would have to look back, in honesty.

To give you a rough estimate of the kinds of things we are talking about, digoxin typically is said to have a low therapeutic index. That means the concentration which produces some type of abnormality, for example, a rhythm disturbance, is not all that much greater than the concentration which will produce efficacy or the desired therapeutic effect.

Q. Therapeutic effect, yes.

J.5

A. A fairly large number of patients manifest digoxin toxicity. This is true particularly in clinical settings where you have outpatients, again, with the issue of potassium-related problems, because a fair number of patients -- it does not apply quite as much in paediatrics as in adult medicine, where the patient goes home, is on a diuretic, is losing potassium, keeps taking the same dose of digoxin and yet comes in severely digoxin toxic and may die as a result of an imbalance in potassium and digoxin levels.

Is this a rare event, no, it is not. It is a frequent event. In a general sense, one has to be reasonably concerned in using digoxin despite the fact that we use it safely in a large number of patients, that toxicity may result.

One situation which can result in sending patients home from hospital as they are getting better, and this has happened with children as well, if they are on oral digoxin, when you are in heart failure, the gut is not as well profused with blood and often absorption is very bad. When the patient gets better, suddenly the gut is now profused and absorption of the drug can improve tremendously, leading to sudden and excessive digoxin

J.6

toxicity. This certainly has happened in adults, it has been documented in children as well.

So I cannot give you accurate numbers. We could try to go back to the literature. I think we probably could not get accurate numbers from the literature, but digoxin toxicity and even fatalities certainly is not a vanishing event at all.

Q. Well, I limited, or indeed I had hoped I limited my question, Doctor, to fatalities resulting from digoxin intoxication in hospital settings, and you are not able to give me that number, I take it?

A. No, but again, it is not uncommon. It is not uncommon.

Q. Now, you have told us something about the distribution curve of this drug, and in particular, with respect to IV administration. I take it that other routes of administration will produce rather different looking distribution curves?

A. Yes, that is true.

Q. Can you sort of briefly and perhaps in graphic language just give me an idea of the distribution curve I might expect from an oral administration, a therapeutic dose of digoxin?

A. Maybe I will draw it and that

J.7

will make it reasonably straightforward.

Q. Well, all right, except we are not likely to make that blackboard an exhibit.

A. I will verbalize the picture.

Q. All right.

A. Again, this will be taken from children, data in children, and a reasonably standard kind of picture that one would see, here we are talking about hours ---

Q. You are plotting hours along the bottom of the graph.

A. We are plotting hours versus serum digoxin, and we will look at a range of -- let me get the actual numbers so that we are not -- I can give you a rough ---

THE COMMISSIONER: I think what we really want to know is whether the angle will be more or less acute; that is all we are after.

THE WITNESS: Yes, it is dramatically different, in fact.

Okay, this is a situation where a 10 microgram per kilogram oral dose was given to children. That is again a reasonable therapeutic type of situation.

What happens is that the blood levels

J.8

gradually rise -- this will be 1, 2, 3, 4, say, 5 nanograms per ml, and the blood levels gradually rise with a peak occurring at about an hour. So this is a very different situation than when it is given intravenously and it immediately enters serum.

The gut has to absorb it, it has to get past the liver, some of which is excreted, then it has to get into the general circulation. So that there is a gradual rise with a peak, and the peak can occur anywhere from one to three hours after administration. It is reasonably variable and can be influenced by food to some extent, by the acidity of the stomach to a limited extent, and little babies do not have acid in their stomach, they have an alkaline stomach, and it can influence it somewhat, by the motility of the gut, and potentially by the disease itself. As we have said when you are in cardiac failure absorption is often not very good and improves as the function of the heart improves. Then it comes down from there with what will be a reasonably standard half life for elimination.

So the beta elimination phase from the body is going to be reasonably similar. Again, we are talking half lives ranging from 20 to 80 hours, and it is then going to be excreted.

J.9

The peaks, in a general sense for a therapeutic dose that we usually talk about is anywhere up to about a fivefold increase in serum concentrations over what it will be at steady state. So that if our steady state concentration in a patient taking 10 micrograms per kilogram per dose per day, as a therapeutic ongoing maintenance dose, and his serum level would end up being 1 nanogram per ml, when we sample it at 12 to 24 hours after the dose, we might well expect concentrations in the range of 5 nanograms per ml at the peak. It is going to be very variable.

THE COMMISSIONER: At what point do you reach the steady state, though?

THE WITNESS: Under circumstances like this, we usually will advise to wait at least six hours in patients.

THE COMMISSIONER: Not that much different than, I guess ---

THE WITNESS: Not that much different but a little bit longer. In a general sense, we are happier if we wait 12 hours because then we are reasonably confident that doses are going to be reasonably at steady state.

Now, if a child is, say, getting a dose twice a day, which sometimes is done, the dose

J.10

will be divided up 5 micrograms per kilogram twice daily, we recommend to the staff that a level be taken immediately prior to the next dose and that this will be a reasonable representation of a level out here rather than getting confounded by a rising or a falling level.

THE COMMISSIONER: But that is not just for oral? You recommend that for all?

THE WITNESS: Yes, particularly for oral, though, because this can be skewed quite a bit more.

THE COMMISSIONER: But I think I have heard that this recommendation has been made and has been adopted --

THE WITNESS: Yes.

THE COMMISSIONER: -- in the Sick Children's Hospital before giving the next one?

THE WITNESS: Yes.

THE COMMISSIONER: Do you happen to know the ratio of intravenous and oral injection?

THE WITNESS: What we have to deal with there is something called bio-availability. In other words, if you give it IV or give it orally, how much total is absorbed from the oral?

THE COMMISSIONER: No, I really want

J.11

to know the percentage of children, if you happen to have this information, given it orally and how many are given it intravenously. If you don't know, that is fine.

THE WITNESS: I do not know offhand. Very often when the children are the sickest, they will be receiving it intravenously because of questions about absorption and vomiting and everything else from their disease.

Clearly, all children who are at home are going to be receiving it orally. What percentage on any given day on the ward I honestly could not say. We could get that information if you would like it.

THE COMMISSIONER: No, no, I do not want it, thank you.

THE WITNESS: Now, intramuscularly, which is another ---

MR. LAMEK: Q. Could we pause there for just a moment, Dr. Spielberg.

Certainly as between oral and intravenous administration, I take it the two major differences between the distribution curves that you have plotted for us are one, that the peak occurs in the case of oral administration approximately an

J.12

hour after administration as opposed to immediately after administration with IV?

A. Correct.

Q. And second, that that peak, when it occurs on oral administration, is nowhere near the height that it is with IV?

A. Yes, that will be, generally speaking, true.

Q. And indeed would be approximately of the order of five times the maintenance level --

A. Right.

Q. -- that you are seeking to achieve on oral administration rather than scores of times higher on IV?

A. Yes.

Q. Now, do we need to bother about intramuscular administration? I gather that is not frequent?

A. Yes, it is not frequent. I think we should at least say something about it.

The situation where one might give an intramuscular injection is where the patient's veins simply are such that one cannot get an intravenous line into the patient at the particular time and his dose is due with the notion that, well, we will put

J.13

the IV in later, we simply cannot find a site at this moment and he needs his medicine, and where, for one reason or another, you cannot give it orally, for instance, if the child has NG drainage and has been vomiting all along from another cause and you are simply concerned that it will not go in.

The intramuscular route, in general, produces rather erratic blood levels. It is absorbed very differently, shall we say, from time to time, from site to site.

K/DM/ak

It can give you blood levels that really are rather difficult to interpret from one patient to another. The other problem is that the vehicle that the drug is in can cause a lot of muscle pain, so we usually do not like to do it but under certain circumstances one might.

If you were trying to estimate what kind of curve you would get, again because of the erratic absorption it is very hard to know, it gets to be somewhere between intravenous and oral, but with so much variability I think it will be very hard to interpret.

Q. Could you give me even an approximate length of time between administration and achievement of steady state distribution by intramuscular administration?

A. It is so variable I honestly don't think you can. To give you an idea how difficult it is to predict, for instance if you give a reasonably large volume it may just sit in muscle and you are absorbing the outer portion that is exposed to circulation, so you have this glop in essence of drug sitting there which can't be absorbed.

If there is already a degree of muscle damage from poor profusion or whatever, it

K2

could sit there for a very long time before it is absorbed. So I think it would be very hazardous to guess, there are no clinical studies using it that way because it is not just a prefered route of administration.

Q. Can I ask you please about Exhibit 217-4 which was your table of relationship to tissue, do you have it?

A. I'm sorry for the disorganization here.

Q. That's all right.

A. Yes.

Q. Do you have it?

A. Yes, this is the serum tissue, age dependence, et cetera?

Q. That's right. I thought I heard you say, Dr. Spielberg, that - this is at a time when you thought the measurement, the numbers recorded levels rather than ratios, that those levels were expressed in micrograms per gram. Now, if that be so, that is a new mood of expressing measurements of dixogin in tissue to this Commission at least, the results that we have seen are expressed in nanograms per gram but micrograms is a method that is used is it, per gram?

K3

A. Basically all metric conversions are inter-convertable.

Q. Yes.

A. For instance, if you were dealing with 125 nanograms, that is .125 micrograms. It depends on what purpose you are trying to use the other data for. If you are trying to sum up all the amounts for total body digoxin you would use micrograms because you end up expressing it as micrograms. If you were looking at tissues that have very small quantities it is better expressing it as nanograms because you might be dealing with 4 or 5 nanograms which is .005 micrograms.

Q. I confess I was a little puzzled with the proposition that you originally formulated that 84 to 325 represented numbers of micrograms in tissues.

A. Yes.

Q. We have cleared that up?

A. Clearly incorrect, yes.

Q. Now we have what they really are, which is the ratios?

A. Right.

Q. In each of these cases you have expressed the range of ratios?

K4

A. Right.

Q. Of tissue concentration to serum concentration?

A. Right.

Q. Do you know what the serum levels were in each of the three studies that you have ---

A. They varied quite a bit. In the latter study, particularly - and again I would have to pull the precise paper.

Q. Yes.

A. In the latter study, the 1983 clinical therapeutics paper most of the levels were rather low therapeutic. In the other papers they were more or less therapeutic in some, and I honestly don't remember in the 1975 paper I would have to go back, very few were, I don't think anywhere in the range for example of some of the concentrations that we will have to deal with shortly.

Q. As you have said of course these studies were conducted, particularly the living studies were conducted where there was no need to be concerned that the distribution might still be in the alpha phase or anything of that sort. Because I take it during the alpha phase the relative

K5

concentration, tissue to serum, can be grossly distorted.

A. That's true.

Q. They may be very similar?

A. Exactly. One could achieve, given again the shapes of the curves.

Q. Yes.

A. The basal variability in the steady state situation you would have to add on a tremendous amount of additional variability due to the alpha phase.

Q. One thing does interest me though, and that is that although three ratios, three ranges of ratios are expressed in each of these studies, or one in each of these studies, the upper end of that range of ratios is remarkably consistent from one to the other, is it not?

A. It is reasonably so; it is reasonably so.

Q. 325, 363, 340. The lower end seems to be all over the map, it ranges from 2.4 times tissue to serum to 84 times, but the top end is reasonably consistent between the three.

A. There are other papers where that range is different on the top side, and again

it becomes hard to know, it is interesting that these three studies actually end up pretty close.

It is very difficult to know, for example, when somebody gets a number that is much higher than these, whether that results from some error in experimental technique, or in fact that results from a patient who in fact has a level that is way outside of that range.

Q. Does the consistency in the upper end of the range of ratios suggest there may indeed be saturation of binding sites in heart tissue?

A. I wish I knew in the hard sense. In the strictly pharmacological sense you can't really use the data that way, because you don't know what would happen if in an individual patient you manipulated his level up, serum level up, and no change - the experiment you would have to do would be to manipulate the patient's serum level up and see no change in his cardiac level, and that has not been done. It suggested that there may be, and the problem again is if we use an analogy to most of the drugs that we commonly use, either metabolic enzymes or receptor sites or whatever, can indeed exhibit saturation, and most of the studies are done

K7

in inbred animals where most of the animals have the identical genetic background and they all saturated at the same level.

When those studies then are converted into human studies and you start looking at what is basically an out-bred popuplation of humans, you begin to see tremendous variability in saturation. For example, in an anti-convulscent like dilantin some patients will saturate their metabolic capacity at 10 migrograms per ml., others at 20 micrograms per ml., others you can go up into concentrations that you would never even use clinically and they still don't saturate. So there is bound to be big ranges which we are used to in our clinical practice but even scientists who use animals are not used to in their practice because animals don't show anywhere near the variability that humans do.

Q. I take it, Doctor, the answer to my question is, no, you can't infer saturation.

A . You can't, I'm sorry about that.

Q. You referred to the redistribution of the postmortem multiplier that has been observed, and you suggested that may also happen during life in certain pathophysiological conditions.

K8

In terms of postmortem relief, levels focus on that, because I understand that is what has been documented to date. In terms of postmortem relief I take it that the loss of binding continues from the point of death and continues for some period of time as cells lose their ability to hold on to whatever is attached to them or within them.

Does it follow from that, Doctor, that in terms of the postmortem multiplier effect that comes from loss of binding, that the closer to death the sample is drawn the less the unbinding that may have occurred at that point in time?

A. That probably is true. In a practical sense though the number of variables that regulate that process is so great that you end up swamping time effects. There seems to be at least from some data that I have seen accumulated from our pathologists a slight increasing slope with time post mortem. It certainly is not in the least predictable. If you looked at the pattern it would be more like a shotgun blast, points all over the map with a slight tendency towards increasing. That is again because of the variability that exists. There are some patients who simply don't elevate their levels post mortem, we don't know why that is. There

K9

are some patients who elevate much, much more than is in the published literature, and we don't know why that is.

You would have to make a list again very similar to all the kinds of things that we talked about before that can influence binding, from disease state, to ions, to genetics, to age. Basically you have so many variables that can't be controlled in a scientific experiment. Usually when we do a scientific experiment we alter one variable at a time to see what effect that variable has.

In patients we just can't do it. We can't isolate those critical variables so we then can see when we go from that patient to a second patient what the critical variables are. I wish we could, it is a terrible problem that we face all the time when not knowing all the variables we can only make reasonable guesses. So in terms of time there probably is a tendency towards times, but there are so many other things going on that it doesn't help you very much.

Q. You referred to what has been going on in your Pathology Department over the last two and a half years. I take it that it has become routine in the Hospital, since late March of 1981,

K10

to draw samples on autopsy of children who died on the cardiology wards for digoxin assay, and those samples are drawn at autopsy and it may be impossible, and I am sure it is impossible to catalogue all the characteristics of each child.

Do I take it - well, let me ask you rather than taking it; are you aware, Dr. Spielberg, whether in those two and a half years a postmortem level of 72 nanograms per millilitre has been recorded?

A. As far as I'm aware to date, no.

Q. Of 78?

A. I believe the highest levels we have seen is in the neighbourhood of about 36 nanograms per ml. Again what we are going to have to do to understand the 72s and 78s is to look at each case clearly.

Q. Yes.

A. Which may give us some understanding of why we have, or maybe why we might expect to see future levels that might even be that high. We will have to look at each case before we can really get into the critical issue of why we haven't seen a 78 but we have seen a 36.

K11

Q. At leas t my understanding, as of October 24th, 1983, there has not occurred in the postmortem assays conducted at the Hospital, whatever combination of events and circumstances prevailed on March 21st, 1981, to produce a level of 78.

A. Actually I do have to correct myself, I am wrong, there has been one value 169.

Q. What was that one?

A. Which ---

Q. That is the gutter blood?

A. Yes. So there is one value of 169 that has been obtained subsequently.

MR. SCOTT: That is the other gutter sample.

MR. LAMKE: I am sorry?

MR. SCOTT: That is the other gutter sample.

MR. LAMEK: Yes.

MR. SCOTT: The first gutter sample was 72.

MR. LAMEK: I said the gutter study, Mr. Scott.

THE WITNESS: Yes. We have to at least state we had one value produced in that range.

MR. LAMEK: Q. You're quite right.

K12

A. And I forgot that as we were going through.

Q. You haven't had that combination of events that produce, whatever it was the 78 in Allana Miller on March 21st, or the 69-71 in Cook on March 22nd, 1981.

A. We have not seen those levels, that is correct.

THE COMMISSIONER: How much was this gutter level?

THE WITNESS: 169.

MR. LAMEK: That was in Mr. Cimbura's data last week, Mr. Commissioner.

THE COMMISSIONER: It passed over my head that's why I didn't remember it.

THE WITNESS: I forget it too. And it is not a good number to forget.

MR. LAMEK: Q. One other matter arising and then coming to the magic hour, Dr. Spielberg. You referred to the capacity, the ability to withhold digoxin as the single most useful diagnostic aid that is available to you in the clinical context.

A. Certainly a terribly useful one, yes.

K13

Q. And as I understood you you were saying the inability to do that with these numbers to see what effect withholding would have on them seriously handicaps the ability to place some sensible and reliable interpretation upon these numbers.

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A. If we could have done that.

Q. Yes.

A. Which obviously wasn't possible, it would have helped, certainly.

Q. Clearly however you could not have done it with Justin Cook, could you, or with Jordan Hines or with Stephanie Lombardo?

A. No, exactly.

Q. Or with Jessie Belanger?

A. Exactly.

Q. You can't withhold what is never supposed to have been administered?

A. Precisely. Or if you find somebody with a level, for example, who received an inadvertent dose of digoxin.

Q. Yes.

A. You know what the circumstances are and you can in fact document then as the blood level comes down whether there are symptoms.

Q. Yes.

A. Example: a child came in with digoxin injestion from his grandmother's digoxin, had a steady state serum concentration of 14 nanograms per ml.

Q. Yes.

L2

A. He had a little bit of vomiting and a slight bradycardia. As his level came down at 7 nanograms per ml he was entirely asymptomatic. So, under those circumstances, number one, we knew that he had taken his grandmother's pills, number two, we could very reasonably assume that his nausea and vomiting and slowing of heart rate at 14 was due to digoxin but strikingly at 7 nanograms per ml, which is an incredibly high level, he was asymptomatic.

Q. Yes.

A. But here we have a good correlation between an event, a level and now clearly as you say there is no way that that could have been done in the circumstances of the children that we are talking about.

Q. Sure.

Mr. Commissioner, I am about to go on to something else, is this the right time to break for lunch?

THE COMMISSIONER: Yes, until 2:30 then.

MR. LAMEK: Thank you.

--- luncheon recess.

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--- on resuming at 2:30 p.m.

THE COMMISSIONER: Yes, Mr. Lamek.

MR. LAMEK: Q. Dr. Spielberg, there is one other area that I wanted to touch on before we get to the individual children.

In the summer of 1982 Dr. Bain who was formerly Chief of Pediatrics at The Hospital for Sick Children conducted a review of the children who had died on or in association with the cardiology wards in the Hospital between July 1980 and March 1981. You are aware of that of course?

A. Yes.

Q. Now, Appendix 2 to Dr. Bain's report -- that, Mr. Commissioner, is Exhibit 48. I don't know whether there is a spare copy for the witness.

Appendix 2 is entitled "Summary of Clinical Pharmacology Review of Patient Records and Transcripts at the Preliminary Hearing".

A. Yes.

Q. Now, Dr. Spielberg, were you one of the participants in that review?

A. Yes. As I indicated at the outset this resulted from an initial series of meetings in the Research Institute where my division

AA2

was asked if we could do a rather quick review of what was known, what wasn't known of several of the charts and also at that time to suggest areas that might need further examination for the future.

Q. And I take it that you were one of the authors of the summary?

A. Yes, that's true.

Q. Without being unduly modest, Dr. Spielberg, to what extent were you the author of this summary?

A. Looking back at this specifically, I probably wrote a fair amount of it with input from the remainder of the division. We met several times as a group, fellows, kicked around various possible ideas and issues. I wrote one complete summary and I'm not actually sure if Dr. Bain included my final summary or it is slightly edited. But basically it would be taken from what I had written.

Q. All right. Well, I have a few questions about it and perhaps you can help me.

A. Surely.

Q. In the first paragraph you set out the background of this matter and note that the group:

AA3

"We have reviewed the charts on Babies Cook, Estrella, Pacsai, Miller and Inwood and the pharmacology and toxicology data presented in the transcripts..."

That is the transcripts of the preliminary hearing?

A. Yes.

Q. "...and the testimony of those three named people and other pertinent parts of the transcript."

And then you go on under (1):

"Assuming that the digoxin blood or serum levels obtained either during resuscitation or post mortem on Babies Cook, Estrella, Pacsai, Miller and Inwood are correct, there are several possible explanations for how such levels may have occurred."

And I pause only to say this. Is it now your understanding, Dr. Spielberg, that at least so far as Pacsai was concerned there was a sample obtained before any resuscitation efforts were undertaken?

AA4

A. Yes.

Q. Yes. Now, you observed that Dr. Hastreiter and Mr. Cimbura both concluded:

"The amount of digoxin which had to be administered to achieve the blood levels found in several of the infants had to be many vials of adult strength digoxin or ten times as many vials of pediatric strength digoxin."

And there was of course evidence, particularly from Dr. Hastreiter, to that effect at the preliminary inquiry?

A. Yes.

Q. I am interested in the last sentence of the paragraph:

"The calculations appear to be based on a steady state volume of distribution of the drug in the range of 10 litres per kilogram."

Now, you have told us this morning about steady state and so on. Can you tell me, in linght of the levels that we are talking about and recognizing that in Inwood at least the recorded level was 491 nanograms per millilitre, is it

AA5

rational to assume that those recorded levels represent steady state levels?

A. We will have to go through in each of the patients because there again may be differences amongst the patients. It becomes somewhat unlikely, given some of the things that we will have to go through, we have major concerns in fact and one of the impetus is I suppose behind looking into the pharmacology was our basic concern that if in fact all the calculations had been based on steady state then in fact there might be alternate ways to explain the levels; the first and most direct being pharmacokinetic, in other words, they were not steady state concentrations.

Q. And indeed, fairly, did it not appear to you likely, perhaps with the exception of Inwood, that the levels recorded probably were not steady state levels?

A. Our initial approach was to make no assumptions whether they were or not.

Q. Yes.

A. But rather based on hypotheses everywhere from steady state to immediate administration, what the pharmacologic constraints were.

AA6

Q. Yes.

A. Given that we had no other way of corroborating, or no other corroborative evidence of timing.

Q. Okay. My question I said, with the exception of Inwood, of course, I should have said particularly with Inwood.

A. Yes.

Q. They were not steady state?

A. Yes.

Q. On page numbered 39, the second page of Appendix 2 --

A. Yes.

Q. -- in paragraph lettered (d) --

A. Yes.

Q. -- it is said:

"Based on the review of the case records, analytical data on digoxin, weight of the patients and the pharmacokinetic literature, several alternate explanations in addition to Dr. Hastreiter's exist for the blood levels which were found."

Dr. Hastreiter's explanation, as I recall it, and tell me if our recollections coincide,

AA7 Doctor, was that massive overdose of the order of many, many vials of this preparation had caused the deaths of these children?

A. Yes. What we were seeking were potential alternate explanations for how such occurred or could have occurred.

Q. And the first one that you set out is:

> "All blood levels obtained can be explained by administration of a single vial of digoxin. For most infants a single vial of adult strength is 0.5 milligrams shortly before death by intravenous bolus."

I know you said something to that effect this morning and I want to be sure, does that include the Inwood level of 491 nanograms?

A. I believe it does. We are going to have to, and unfortunately as I explained to you, since my testimony, the announcement of my testimony was rather recent, I haven't had the chance to go back and redo all the calculations.

Q. Yes.

A. As we approach that specific baby we can go back and recalculate it. I believe

AA8

that it does but I would want to be absolutely sure when we arrive at that baby.

Q. Fine.

A. Her weight, et cetera, that we go back and redo the calculations.

Q. And I recognize that consequently on that page you say the data do not permit exact timing of administration.

A. Yes.

Q. But implicit in the proposition under (i) is that you do have some feel for the period prior to death, that is, a dose of the magnitude that you posit may have been administered inorder to produce those levels. You say, "...shortly before death by intravenous bolus".

Can you give me any idea of the kind of interval you had in mind?

A. By shortly in the broadest sense, and again we will have to look case by case. There are several possible times. One would be shortly prior to arrest and conceivably even after arrest, during a resuscitation process.

Q. Right.

A. The shortest period of time then I suppose would be indeed during a resuscitation

AA9

process after the baby had arrested and then when we are talking about how much before circulation has ceased, then we have to deal with basically our kinetic curve and try in each instance to model back in a reasonable sense how far we can talk about it, and it is going to vary with each child.

Q. Sure. Now, if you are talking about administration prior to arrest, does that contemplate that the administration may have caused the arrest?

A. It might or might not.

Q. Yes.

A. In other words, if under certain circumstances the blood level were extremely high and yet distribution had not occurred into tissues to cause the direct toxicity, then one might not expect that to be the case.

Q. Understood.

A. On the other hand, if some distribution had occurred into tissues, indeed, it may have been the direct cause of the arrest.

Q. Fair enough. Equally though may I take it that in the event that administration occurred after arrest it could not have caused the arrest?

AA10

A. Yes.

Q. Although it may have contributed to the death?

A. Yes. In that, for example, if the administration occurred during a resuscitation effort and tissue entry had occurred, it might have made the resuscitation less successful, or at least decreased the possibility of the resuscitation having been successful.

Q. Now you said a moment ago that it may have occurred prior to the arrest or, and I think I remember your word exactly, conceivably after arrest and during resuscitation.

A. Yes.

Q. Does your use of the word "conceivably" suggest a lower order of possibility for post arrest administration in your mind?

A. Again, we are going to have to go case by case. I can't really distinguish between those two possibilities in any strong suggestion, you know.

Q. Yes.

A. In any strong magnitude one way or the other. It depends to a certain extent I suppose on the mechanism by which, if a dose was

AA11

administered, how it was administered.

Q. All right.

A. And we will have to again really go by case in terms of that.

Q. Yes. Let me understand something about the mechanics of what is happening in the body in the period from arrest to eventual declaration of death.

I think I have understood you to say, Dr. Spielberg, that digoxin in the serum before it has yet reached the tissues is not pharmacologically active. That is not what is going to do the damage in terms of toxicity.

A. This is our basic presumption.

Q. Yes.

A. Yes.

Q. And therefore can I think of the circulatory system as the transport system?

THE COMMISSIONER: Excuse me, basic what?

THE WITNESS: Assumption that digoxin not at a receptor is not going to have any pharmacologic activity.

THE COMMISSIONER: That's a

AA12 reasonable assumption, isn't it? Have you any doubt about it?

THE WITNESS: I suppose that the only caveat one would put in, and I think it is not a major one, is that if some of the effects are mediated via the central nervous system rather than binding to the heart we don't know really almost anything about those central effects. However, we are dealing primarily with events at the level of the myocardium or the cardiac tissue per se and certainly those events are going to be mediated by receptor binding and high levels in the serum are not going to be reflected by toxicity unless there is digoxin occupying receptors.

THE COMMISSIONER: Yes, all right. Go ahead.

MR. LAMEK: I have forgotten my question.

THE COMMISSIONER: Well, the question was what led up to it when I interfered.

MR. LAMEK: Ah, yes, I have it.

THE COMMISSIONER: The serum will do no harm.

THE WITNESS: I mean, for all practical purposes I think that it is our best working

AA13

hypothesis that we have got at this juncture.

MR. LAMEK: Q. Okay. Operating on that hypothesis, may we then or may I then properly treat the circulatory system as a transport system?

A. Fairly reasonably, sure.

Q. Okay. Now, what happens to that transport system at the moment of cardiac arrest? Does the transport system grind to a halt?

A. It depends on the arrest.

Q. All right. Give me the range of possibilities.

A. Now, for example, if one achieves asystole.

Q. Yes.

A. Which means no heartbeat whatsoever, then there is going to be little if any blood circulating. If the phenomenon that leads to the arrest is basically bradycardia, or slowed heart rate --

Q. Yes.

A. -- then blood is still circulating but it is circulating at a slower rate, but circulation is still occurring. Similarly with a number of ventricular arrhythmias, if a patient

AA14 develops a rapid ventricular rate, efficiency is not at all as good but there is still blood circulating.

THE COMMISSIONER: Before you go on.

THE WITNESS: Yes.

THE COMMISSIONER: Doesn't an arrest mean what it sounds like? Doesn't it mean stopping?

THE WITNESS: No.

THE COMMISSIONER: It doesn't?

THE WITNESS: Not really.

THE COMMISSIONER: We have heard these terms bradycardia and tachycardia and ventricular fibrillation but I had always thought that cardiac arrest means the stopping of the heart.

THE WITNESS: Well, only in a generally loose sense at the time that intervention occurs.

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If a heart rate is slowing progressively in fact an arrest team may be called, a 25 call.

THE COMMISSIONER: Yes, I know about arrest teams, but I am talking about cardiac arrests. When somebody uses the term "cardiac arrest", they do not mean cardiac arrest I take it?

THE WITNESS: They do not necessarily mean asystole. They do not necessarily mean no heart beat at all. In fact, the rhythm at the "arrest" as found by the arrest team may be one of a number of different potential arrhythmias, most of which are usually severe enough so that certainly circulation is markedly impaired and it may vary, of of course. So that you do not have to have no heart beat to require resuscitation. You can have ventricular fibrillation, under which circumstances profusion of tissues is extremely poor, very little blood is circulating, some is, and yet under those circumstances, one would consider the patient to have had "an arrest".

MR. LAMEK: Q. Perhaps I can express it in this way, and I am not sure how far I can push this, whatever it is, a simile or whatever the other one is. In the case of a true arrest strictly so-called where there is asystole then I take it

our circulatory transport system stops?

A. It would presumably not be working.

Q. Yes, and therefore, not carrying digoxin which is presently on it to tissues?

A. Right.

Q. In the case of a situation which is considered to be so serious as to justify the calling of a Code 25 and the undertaking of a resuscitation effort, even though asystole has not yet been reached, then either because of some ventricular arrhythmia or dysrhythmia or extreme bradycardia, the transport system may still be travelling but not very fast and not very effectively; is that fair?

A. Presumably at the moment the team arrives, yes.

Q. Now, if I understand it, the object of the exercise, the primary object of the exercise in resuscitation is to get normal rhythm going again?

A. But the initial effort is to provide oxygen to tissues and that ---

Q. To get the circulation

moving?

3 A. Yes, which is usually No. 1, to provide oxygen and ventilation to the lungs, and No. 2, until you have established normal heart rate or normal heart rhythm, to manually pump the heart to deliver blood to the tissues.

Q. Keep the blood moving around delivering oxygen to the tissues?

A. Exactly.

Q. But I take it that, too, is a less than perfect way of continuing circulation. It continues but not ---

A. Not ideal but in fact to maintain tissue viability and profusion and certainly patients -- for example, the brain is usually the organ most sensitive to loss of nutrient and oxygen and certainly doing manual CPR or cardiopulmonary resuscitation can maintain viability of that organ for a period of time.

Q. Obviously the point to which I am fumbling and labouring my way, Dr. Spielberg, is this: is it reasonable to say that during resuscitation efforts, the functioning of the transport system, circulation, is not as effective and efficient as it is in the normal child pre-arrest?

A. In a general sense I would

4 say that has to be the case, except if during a resuscitation the child re-establishes heart rate and then loses it again.

Q. Of course, yes.

A. And during CPR you have a reasonable tissue profusion. I cannot give you accurate numbers in terms of percentage profusion certainly.

Q. All right. Now, let us take the point either at the initial arrest or upon the inability to restore proper heart beat, death is pronounced. At either of those points you have got a close down of our circulatory system?

A. Right.

Q. And at that point we do not have any further delivery of digoxin or anything else in the blood to organs and tissues.

At what point thereafter might one expect to see the unbinding begin to occur?

A. No one has any idea, sadly. There are no data to address it, no data whatsoever.

Q. We cannot tell; we have no idea?

A. We really cannot.

Q. It could be immediately, there could be an interval of time?

A. And my guess would be that it would be so variable that no unbinding would occur for hours post mortem in some patients, and perhaps earlier on in others. Basically, again, the number of variables occurring at the time really do not allow one to say much.

The flip side is again when we are talking about unbinding, we are not talking about 100 per cent release,we are talking about two, three, five, ten per cent release with 90 per cent bound, and under those circumstances I think one would be very foolish to try to predict what kinds of time courses or what kinds of release or what kinds of ability to bind would go on during that interval. We just do not have the data.

Q. All right, I understand. I take it, though, that one of the ways by which a drug like digoxin could very effectively and efficiently be carried to the heart during resuscitation is if it were inadvertently administered by intra-cardiac injection?

A. Yes.

Q. That is one possibility?

A. And many drugs are administered in an urgent situation via cardiac

injection. Perhaps many less now than back in the time we are talking about in that we now have a good deal of literature on the use of medication such as epinephrine or atropine, given the endotracheal tube where it can be literally pushed down into the lung where it is absorbed very, very rapidly and the pulmonary circular bringing it immediately to the heart. So that one certainly could achieve very high concentrations within cardiac blood if it was given intracardiac, recognizing that the practice probably was more common in the past than it is now.
6 But it certainly happens now as well.

Q. And indeed, that led, did it not, to your point under (iii) on this same 1 page where it is suggested:

> "...several different hypotheses have to be considered in interpreting the blood levels in terms of amount, timing, and intent. It would seem unlikely that administration of multiple vials by accident could occur. If, however, a single vial can account for the levels achieved, then either accidental or intentional overdose is a possibility. Vials

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"of digoxin resemble vials of many different emergency medicines, and there is ample literature on confusion of ampoules of different drugs in a variety of clinical circumstances."

Do I take it that one of the circumstances which you are perhaps suggesting in the course of making that observation was the circumstance of a resuscitation effort?

A. Conceivably, or pre-resuscitation changes in the patient which would have led to a lot of activity attempting to prevent an arrest from occurring.

Q . You then go on to observe that the blood and tissue levels of digoxin by themselves are not likely to be helpful in pointing in one direction rather than the other, and that there are several significant methodologic problems in determination of digoxin content of postmortem samples and so on, and as I am sure you know, Mr. Cimbura agrees with that.

Now, on the next page, perhaps we should -- you are pointing out the many variables at the bottom of the preceding page which make

interpretation difficult?

A. We have subsequently learned that there are many more than we were then naive to.

Q. But there are no fewer now than there were then?

A. Yes.

Q. At the top of the next page, one of them is one you point out:

"(2) analytical problems: radioimmunoassay versus high performance liquid chromatography..."

Let us pause there for a moment. Why RIA versus HPLC?

A. It was not meant as one in contrary distinction to another. The issue that we were addressing with respect to that is an issue that in one of the figures that I handed out was actually carried out. That is measuring specific digoxin, which means in this situation doing an initial extraction, usually with an organic solvent, taking digoxin out of the aqueous or serum phase into the organic phase, drying it down, passing it through a high pressure liquid chromatogram to separate it from other compounds and then doing an RIA as opposed to doing, the radioimmunoassay on whole serum.

Q. I take it you regard the former as more desirable than the latter?

A. Well, it depends what you are looking for.

9 Q. If you are looking for digoxin.

A. But you are not -- it depends what you are looking for. Let me say what that means.

If you are trying to measure digoxin, pure digoxin, if that is your goal in mind, then having a reasonably purified sample is a useful goal.

If you are trying to extrapolate from a serum sample how much drug may have been given, then pure digoxin determination may not be your goal. For example, let us say a patient is metabolizing a significant fraction of the digoxin to compounds which interact more with an RIA, for example, digitoxigenin and some other metabolites, give you more RIA positive material while other metabolites give you less.

If you want to say something quantitatively or try to, in any case, a back extra-polating to a dose of the drug given, then you would want to know something about not only digoxin but about all the other substances present. So that again,

depending on your goal, different techniques have different applications.

If you want to know about active cardiac glycoside, you then want to measure digoxin and active metabolites. If you want to know about the whole story, you want to measure digoxin and all metabolites. If you want to know about digoxin only but not to back extrapolate to doses or anything else, you want to measure pure digoxin and then you can say what contribution the pure digoxin makes to the over-all picture. It is not meant to be confusing but it is an important point.

Q. No, I do not think it is confusing, Dr. Spielberg, but do I take it, being a bloke who likes to get two for one if he can, that it may be that for multi-purpose enquiries, perhaps the happiest solution would be to do the RIA, measuring digoxin and metabolites all, then do an HPLC and then do the testing from the extracted sample?

A. An ideal profiling would include that plus mass spectroscopy and identification of all the metabolites and taking into account the extrapability of each of the metabolites.

For instance, when you extract the serum, you are going to take some of the digoxin,

you are going to take some of the less polar or less water soluble metabolites into the organic phase, and again, one has to be very, very cautious. I think the older literature may be misleading to the extent that it used to be said that only about 15 per cent of digoxin is metabolized in a patient. Some of the
11 newer literature is suggesting in fact with a great deal of biologic variability, as we would expect from any drug, that in fact a much larger percentage may be metabolized in some patients, and in those patients particularly if you wanted to get the whole profile as you suggest you would have to measure total "pure" digoxin, and if you wanted to get an idea further about the activity of the serum, you might want to do one additional thing which would be to examine the effect of the serum on where digoxin works. For example, you could take the serum and put it on red blood cells and ask how much interference with the sodium ATP ase occurs. That will be done with rubidium uptake studies, and in fact, the most recent literature suggests that if you couple rubidium studies together with blood level studies together with metabolite studies in living patients, it gives you a much more accurate picture of whether or not that patient is digoxin toxic.

So that will be the ideal. That is a little beyond the scope of this present investigation, but that would be a not even yet the
12 state-of-the-art ideal but close to it.

Q. I am interested in the way you end your paragraph immediately prior to the recommendation section, Dr. Spielberg. You say:

"Given the difficulties in interpreting levels even if analytically correct, however, we are pessimistic that additional analytical information in the absence of further epidemiologic data will sufficiently aid in elucidation of the etiology of the problem."

I take it that elucidation of the etiology of the problem means provide an explanation?

A. Help us answer the problems and questions that we are dealing with.

Q. What kind of epidemiologic data did you have in mind when you wrote that sentence?

A. Well, again, the problem we were facing and the problem that perhaps we faced to a greater extent now because we know so much more two years after the fact or I suppose it has been about

a year since this was written and we have learned a lot more about how levels can be achieved, is that while we can take the data so far and we will go through each patient and we will try to, as clearly as possible, say how far the data can be taken, in the absence of something else, some other external corroborating evidence, it makes it extremely difficult to interpret the data. The analytical part and the
13 review of each patient hopefully will be able to tell us whether there are, as we said before, a series of patients similar or a series of perhaps different events which occurred in different patients leading to a similar result. To aid in that process, then, one would like some sort of other information, other than the pharmacology, a finding of mechanisms of administration, of a syringe, of something else that allows us to then go from apples and oranges to a cluster of apples.

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Q. I'm sorry, forgive me. It is no doubt my denseness, but I am not really sure that I understand the significance of "a syringe" in the context of epidemiologic data.

A. What we were referring to was non-pharmacologic data. For example, obviously the finding of - and we had no hope that it would happen, given that it hadn't at that point, external corroboration of administration. In terms of the epidemiology our hope was that if we were trying to choose in some situations between, for example, administration prior to an arrest and administration after arrest, if we could get data on survival of arrests it might give us a clue. It wouldn't necessarily answer the question, it would give us an additional clue.

For example, if we could look at the pattern of risks and say, gee, what really seems to be going on with patients not surviving arrests, this might point us in one direction.

If we could get data that said, well, the same number of patients are surviving arrests but more patients are arresting, that might focus one in a different direction.

If there were no change in any of those things, which we didn't then know, but we now know

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in terms of pathophysiology, we might then say, would the pathophysiologic explanation be more reasonable. So it is that kind of focus that we had hoped might then allow us to look at the numbers in context, as a group. The pharmacologic issues being to define individual cases and then to see if we have a forest or a collection of individual trees.

Q. Because the individual cases in themselves may be ambiguous.

A. Precisely, precisely.

Q. By saying if there is a pattern that can be discerned the ambiguity may be resolved, or you may be directed in one direction rather than the other, do I understand you?

A. Yes. In other words, it would help focus things because if we had data that generated or supported a given hypothesis, this then might help us go back analytically and see if we could answer certain questions.

Q. And it was in that context that the name of the Centre for Disease Control in Atlanta came up?

A. Yes.

Q. And now one of the matters which you referred to in the course of this report,

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when I say you are a menial group, you understand that, Dr. Spielberg, was the difficulty of knowing how to deal with levels recorded in exhumed tissues. There you have all the problems doubled and re-doubled in spades, if you like, would you not?

A. Yes, with so many variables that we could not conceive of a way of answering questions with those numbers.

Q. Is there one question which in your opinion can be answered by those numbers, and is it this: That although one may not be able to build back to an antemortem level in children in whose exhumed tissues digoxin has been measured, one may at least say with some confidence that they did have some digoxin administered to them during life.

A. At our present state of knowledge it is probably a reasonable assumption with the following caveat: That has been the issue of endogenous substances.

Q. Yes.

A. I don't want to get into that in great length, I gather the hearing has heard a great deal about it.

The issue is that at this stage of development the so-called natiuretic hormone, which

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people have been looking for 20 years, which this substance may well be, the stuff that causes increased sodium excretion in the face of a failing heart, or a failing kidney. It is not a new thing, I mean, people have been looking hard for 20 years and now we may be getting there. We really don't yet know much about its distribution in tissue, or what makes it go up or what makes it go down, or how high it can go. Until we know that we cannot close the book on the possibility that some of the substances found might be that.

Nor, even if we have mass spectroscopy data for digoxin can we completely close the book on that, because there may be structurally related compounds which have very much similar atomic spectrum, and until we know what compound X, and I hate using the term, but that is what has been used, until we know what its structure is and what its ionic constitution is and what its chemical structure is we can't be 100 per cent sure that it might not have a spectrum very similar to digoxin.

Now, having said that, presumably, and I think when we talk about patients I think we will have to for the moment accept the suggestion that if digoxin by mass spectroscopy is found in a

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patient the likelihood is that they receive digoxin. We can't say anything quantitatively; we can't say how; we can't say why, we can say that it is likely, with the caveat that we may have to change that answer if new data comes in, and we have to always be prepared to do that. How probable is that, I don't know, I really don't know, but for the moment I think we have to work under the assumption that digoxin is present.

Q. You say if identified by mass spec.; what if identified by high pressure liquid chromatography and RIA?

A. It doesn't help any more. There are chemicals ---

Q. It doesn't help any more than what?

A. It doesn't help - well, let's put it this way. The tools that we used, okay ---

Q. Go ahead.

A. Okay, for determining what something is, okay, are either mechanical or organic extractions techniques, or column chromatographic techniques, like HPLC, where we are using the chemical structure of the compound as a tool to separate it from other compounds. The possibility

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always exists and it happens frequently, you know, in situations where we are dealing with standard drugs and such, where something else may interfere which could mean that it travels in the same place on the HPLC because it is chemically very similar, I mean HPLC will not separate every compound from every other compound, where it is sufficiently similar that it interacts with the RIA, or where its structure is sufficiently similar that it confuses you on mass spec. Can that be seen to happen? What is interesting with this new compound and this is data from other sources, not from the Hospital for Sick Children, is that this substance whatever it is, is RIA positive and it appears that it also can interact with the digoxin receptor, with the ATPAs. There is a study now in British medical journals looking at hypertensive patients who appear to have more of this, and in fact it will compete with one of the digoxinlike compounds for binding to red cells. So not only does the antibody to digoxin recognize it but the biological target recognizes it. That means it's awfully similar, including in its tertiary structure, the chemical structure of the substance because it will, if you will excuse the expression, snuggle up to the actual site on the

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red cell as well as to the antibody, which are two totally different things, so it is presumably fairly similar.

THE COMMISSIONER: Doctor, there may have been buried in that answer an answer to the question that was posed, but I didn't get it yet.

MR. LAMEK: Perhaps I should ask it again.

THE COMMISSIONER: What I would like to know is whether if you have the RIA plus the HPLC plus the RIA on that eventual result, if that is likely to produce determination on whether or not digoxin was given to the child, that's all.

THE WITNESS: It is highly likely with the caveat that there still may be something else that is handled in the same way on the RIA, the same way on HPLC, and the same way on mass spec.

THE COMMISSIONER: All right.

THE WITNESS: That is the only honest answer.

THE COMMISSIONER: One is as good as the other of that determination.

THE WITNESS: Well, in fact for this particular, whatever substance it is, it is different than many of the artefacts we deal with because it

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interacts in so many different ways very similar to digoxin.

MR. LAMEK: Q. On the basis of our present knowledge, Dr. Spielberg, may I have it please that a substance is identified, is described as digoxin after HPLC and RIA, the probability on the basis of our present knowledge, what we know now, the probability is that is indeed digoxin? If indeed that is measured in the tissues of a child the probability is that that child was administered digoxin during life.

A. I have to accept that answer with the caveat that I may have to change my mind.

Q. Well we may all have to change our mind, Doctor.

THE COMMISSIONER: Yes.

MR. HUNT: In light of the evidence, Mr. Commissioner, from Mr. Cimbura re the extraction process in addition to the RIA, the HPLC and the RIA method, if my friend could pose that question as well to see what the Doctor's opinion would be if that factor was added into it.

MR. LAMEK: Q. I think I can probably predict.

A. The only real answer is, if

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the chemical structure is extremely similar they will handle very, very similarly. The thing that is scientifically fascinating to us, you know, in pharmacology, is that you have got something that is remarkably similar in that it interacts at both the receptor and into the antibody and there is very little precedent for something like that and it is fascinating. How meaningful it is I would not pretend to know. For the moment I think we have to accept your premise that the probability is that it is digoxin with the caveat.

Q. I am particularly interested in that of course because I understand, Dr. Spielberg that you have reviewed the charts of five children, that is to say, Cook, Miller, Pacsai, Estrella and Inwood.

A. That is correct.

Q. You did not however particularly review the charts of Jordan Hines?

A. No.

Q. Or of Stephanie Lombardo?

A. No.

Q. Or of Jessie Belanger?

A. No, that is correct.

Q. You are aware I take it that in

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the exhumed tissues of Lombardo and Belanger, and in the fixed tissues of Hines, digoxin is reported to have been identified?

A. Yes.

Q. And I take it you are also aware that those three children were apparently not prescribed digoxin during life?

A. That is my understanding, yes, sir.

Q. And I take it therefore on the basis of what we have come to so far, one can probably conclude that in one way or another digoxin was administered to those children during life?

A. Yes. I think, you know from what we have led up to with the caveats put in, I think it indicates that in all likelihood, with some doubts still remaining, that the children received digoxin.

Q. Yes.

A. Some digoxin.

Q. Some digoxin, and we don't know, we can tell how much?

A. No.

Q. Certainly from the exhumed tissue we cannot tell.

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A. Again it is a frustration, we wish we could, we truly wish we could.

Q. I suppose, Doctor, one has to consider how that drug may have found its way into their bodies; and breaking it into broad categories I take it you will agree with me either unintentionally or intentionally.

A. I think that covers the two possibilities.

Q. Well there are two others, one is innocently or maliciously, you can do something intentionally but not with malice; I intend to give him something because he is supposed to have it.

A. This is fair.

Q. Innocently or maliciously.

A. This is fair.

Q. Does it fall within the possibility of innocent administration to those children that they received the drug accidentally in the way in which you suggest it might be possible in the course of this appendix to Dr. Bain's report; that is to say either shortly before or during the course of resuscitation?

A. This is conceivable if the medication error were made under such circumstances.

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Q. Would you advance, Dr. Spielberg, as a serious possibility, the chance of medication error in each of the three children?

A. I think it is not at all unlikely, or impossible, knowing something about what we know about medication errors in general. We don't really have very much data from the Hospital for Sick Children, but there is a great deal of published data from other centres in the circumstances with non-unit dose. Emphasizing again that now digoxin is handled in an entirely different way than it was in the past in the Hospital.

Q. Yes.

A. And in fact unit dose exists which totally changes the picture, so we are talking about a system which did exist at that time which has been changed, and there is ample data from other centres on how likely medication error is to occur.

Q. You are aware I take it, Dr. Spielberg, that one other child of the group with which we are concerned also did not have digoxin prescribed for him, but it was discovered, and that of course is Justin Cook.

A. Yes.

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Q. And indeed to the best of my recollection only 4 of the 36 children who are under review here had not had digoxin prescribed for them ever. Is that your understanding?

A. I really don't know for sure because again I am not familiar with the 36 cases.

Q. Okay. Well, I ask you to accept it from me.

A. I assume that that is the case.

Q. And is the suggested possibility that you are putting, Doctor, that of four children who did not have the drug prescribed, in a hundred per cent of the cases there was some medication error resulting in their receiving the drug?

A. I can't answer that without a lot of other information. Now, what other information do we really need to approach that issue?

Q. Well, let me tell you what we have and you tell me what more you think you need in order to answer my question.

A. Sure.

Q. Of the 36 children who died on the cardiology wards between July 1st, 1980 and March 31st, 1981, 4 had never had digoxin prescribed. In the tissues of each of them digoxin was identified,

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and you have agreed with me that the probability is that one can say they received digoxin during life?

A. Yes.

Q. In the absence of prescribed digoxin that can only innocently be medication error, I take it?

A. Yes.

Q. Therefore each of the four children who was not to receive the drug received it on this hypothesis by error?

A. Yes.

Q. Is that not a hundred per cent?

A. It is a hundred per cent of four. What I don't know is of all the children on the ward, and I don't even know how many total children there were, how many might have inadvertently received a dose of digoxin. The problem is, okay, that we are dealing with - this is a rough estimate - between 10,000 and 15,000 doses of digoxin being administered on a ward like that in a year. It is a lot of doses of digoxin and in order to make an intelligent assessment of potential errors, which happen everywhere. I mean, the data that is published is not Hospital for Sick Children data, it is university hospitals in the States and elsewhere in Canada with

DD.3

error rates that vary between hospital and hospital.

In order to know whether four is a very high number or not a very high number, we have to know the characteristics of those children, we have to know the characteristics of the children that did not receive an inadvertent dose; were the children in fact who received an inadvertent dose, if that was the case, in a situation where there was an increased likelihood of their receiving an inadvertent dose, sicker, next to a sicker child, et cetera, et cetera.

It is a very, very hard thing to get at. From my experience in hospitals elsewhere as opposed to The Hospital for Sick Children, if I were asked that question about the other institutions I have been in and whether there was a reasonable probability that that kind of medication error situation might exist I would have to say it is reasonably probable. How reasonably and how probable I could not put quantifications on.

From my experience in monitoring drug errors at other institutions, which was my responsibility by sitting on the Pharmacy and Therapeutics Committee, again at other hospitals, we have certainly seen runs of incorrect administration, some

DD.4

unrecognized for weeks upon weeks, some because they have no consequences, and one of the issues in medication errors is that the vast majority of them do not have clinical consequences. I mean, it might be a switching for example from one antacid to another. That is an error but it doesn't have an adverse effect on the patient.

Similarly, if a low dose or a therapeutic dose of a drug like digoxin were given to a large number of children, for whatever reason, no adverse event might result and therefore no one would know that they had received the drug.

We had a series of unfortunate instances when I was at Johns Hopkins of confusions between Lidocaine and 50 per cent dextrose.

Despite recognition, actually, some additional errors occurred. How can we try to quantify this? I honestly don't know. I am not an epidemiologist, I don't have the wherewithal to really say. But again from experience at other institutions would I be tremendously surprised? In honesty, no.

Q. Doctor, in the course of Appendix 2 to the Bain Report, you and your group suggested that one possible explanation for these numbers was accidental administration.

DD.5

Of the five children in respect of whom you posited that as a possibility, only one of them is in the group that we are now considering. We are now considering three additional children, not included in those five. Is it your suggestion that the levels in the five and the presence of digoxin in three additional children, that is to say, Hines, Belanger and Lombardo, may all be explicable on the basis of medication error?

A. I think what we are going to have to do is look at each one individually.

Q. Well, would you answer my question and then perhaps you can give me an explanation of your answer.

A. Yes.

Q. Is it your suggestion that the five which you did address in the appendix to the Bain Report, plus the three whom I am now addressing may all be explicable either as to level or as to the mere existence of the drug on the basis of medication error?

A. I think that has to be accepted as a hypothesis. I think there are better explanations in some of the patients than error.

(2) Q. Well, perhaps at the end of the

DD.6

day we will find out how many we have to ascribe to error.

Certainly I take it we have got three in the error category, have we not?

A. Yes.

Q. That is Hines, Belanger and Lombardo because if those aren't error then they are something more sinister, are they not?

A. Or something we don 't understand, yes.

Q. Or something we don't understand, yes.

Okay. Well, perhaps we should turn then to the children but it is 3:30, Mr. Commissioner.

THE COMMISSIONER: All right.

MR. LAMEK: My timing is astonishing.

THE COMMISSIONER: We will take 15 minutes.

MR. LAMEK: Thank you.

--- Short recess

--- Upon resuming:

THE COMMISSIONER: Yes, Mr. Lamek.

MR. LAMEK: Q. Dr. Spielberg, can we turn then to those children whose charts you did review in the late spring, early summer of 1982.

DD.7

A. Yes.

Q. With a view to providing information to Dr. Bain, information that appears in Appendix 2 to his report. I want to go at them in reverse chronologic order, if I may. I understand you have not had an opportunity to review all of the charts in detail for a second time in preparation?

A. Yes.

Q. And therefore if there is anything in the course of any chart that you have not yet looked at and refreshed your memory about,by all means tell me and maybe by tomorrow you can do that.

A. Sure.

Q. But you have at one time reviewed the Hospital chart of Justin Cook, Exhibit 116, Mr. Commissioner. I wonder if the Registrar could put a copy in front of Dr. Spielberg, please.

A. Thank you.

Q. And I may tell you first, Dr. Spielberg, that Dr. Rowe - Mr. Commissioner,this evidence is found in Volume 18 of our transcript at page 3250. Dr. Rowe has said in evidence before this Commission that Justin Cook's death was consistent with his clinical condition and, in particular, with his having suffered what Dr. Rowe called a very

DD.8

classical, very severe blue spell from which he did not emerge. But also at that same page, Mr. Commissioner, and I tell you, Dr. Spielberg, Dr. Rowe did not suggest that the clinical condition or the blue spell was the cause of Justin Cook's death, he said his opinion in late March, 1980 was and indeed when he gave evidence here a couple of months ago still was that Justin Cook died as a result of an overdose of digoxin. That is found in particular, Mr. Commissioner, at pages 3274 to '5 in Volume 18.

He said he regarded Cook's death as unquestionably having been caused by digoxin intoxication.

Now, Dr. Spielberg, do you as a clinical pharmacologist and on the basis of your review of this child's chart and the digoxin levels measured in his antemortem and postmortem blood and in fresh and fixed tissue, do you agree with Dr. Rowe's opinion?

A. To a very great extent I do. I believe that there is strong evidence that this child indeed received a dose of digoxin. We can go through in a moment what the maximum or minimum amounts might be.

Q. Yes.

DD.9

A. He was not prescribed digoxin and therefore we cannot say that the levels or amounts present were due to prior therapeutic use of the drug. The concentrations are high but we have to consider what high means in the context of what we have been talking about this morning. The only place where I would diverge is that I can't be absolutely sure that this really caused his arrest. It may well have. It may have contributed to difficulty with resuscitation if the dose was given at about the time of resuscitation efforts. So that there has to be a bit of a difference between Dr. Rowe and I in terms of being that certain that the digoxin caused the child's demise, or initial arrest.

Q. All right. Are you able to recall or to direct us to anything in the chart, Dr. Spielberg, which in your view is not consistent with the death having resulted from digoxin intoxication?

A. I think there are several things that we should at least consider without again reviewing the entire chart.

Q. Yes.

A. Certainly I think, I haven't read Dr. Rowe's testimony, so, I don't know all the

DD.10

details. Certainly it appears that the child did indeed have a cyanotic spell prior to the time of his final arrest.

Q. That is so.

A. In my notes, and again not having reviewed the chart in months I am not precisely sure, in my notes it says about 1800 on the 21st during which time his murmur changed, which suggested that blood flow to the heart had changed. He became actuely blue, or cyanotic, and at that time he was given a medicine called propanolol, a beta blocking agent which is sometimes used in blue spells. The baby did not have tetralogy of Fallot but the hemodynamics at least to my understanding are reasonably similar and propanolol would be expected to have benefit. And it appeared that the child improved. And then again we are told that about 3:30 in the morning of the 22nd that the child again suffered a severe blue spell.

Now, could the bradycardia and the variety of phenomena which occurred immediately after that blue spell have been due either to his disease state or to digoxin? The answer has to be yes to both. Digoxin certainly could have produced some of these symptoms. His disease state per se also could

DD.11

have produced very, very similar symptoms. So that if I were asked in the complete absence of any information whatsoever about digoxin levels to look at this, I would say, yes, all of this appears to be quite consistent with the patient's clinical course, what we know about his heart disease, the seizure which occurred which may or may not have been hypoxic as a result of the tremendous decrease in oxygen concentration.

Beyond that on purely clinical grounds, in the absence of any pharmacologic data, looking at the case I would say, yes, this appears to be entirely consistent with his course. However, we have digoxin data and we cannot ignore the digoxin data. It would be foolish to even consider such ignoring. The question then is, how did digoxin get to this infant and what kinds of amounts of digoxin might
(3) we be talking about in reasonable sense?

Q. Doctor, just before we address that and it is important that we do.

A. Yes.

Q. I may have missed the answer to my question what you have just said. I think my question was, is there anything in this chart which is inconsistent with digoxin intoxication having caused the death?

DD.12

A. There is nothing in any chart that is ever inconsistent with that conceivable possibility. In this situation, knowing that digoxin is present.

Q. Yes.

A. We have to very strongly consider it a possibility of digoxin.

Q. I'm sorry. Now, you were going on to consider how and to what extent he might have received digoxin?

A. Okay.

THE COMMISSIONER: I am sorry, you said there is nothing in any chart that is inconsistent. You mean in any death in all history that has taken place?

THE WITNESS: Oh, no, for most - many -- let me modify that, certainly that was perhaps a little hyperbolic. Many patients dying of heart disease, the course of their deaths from heart disease are often and almost invariably indistinguishable from many of the same things that digoxin would do. So that purely on clinical grounds with no other corroborative evidence it becomes I think impossible for at least me as a clinical pharmacologist,and you would have to ask cardiologists as well, to say, no,

DD.13

digoxin could not have contributed to this death. In fact, under these circumstances with this baby, we have to cope with the fact that he has digoxin on board.

Q. Yes.

A. And there is no way around that, we must deal with that.

Q. All right.

EE/BN/ak

Now, what are the maximum and minimum amounts that explain the blood levels and then we have to take into account the tissue levels as well, because in this situation as opposed to the other situations, we have to deal not only with the blood level, which the blood level unfortunately is after arrest, we do not have any pre-arrest levels as such, but we do have some fresh tissue, and this is the only infant in whom we have fresh tissue. So we have to deal with the fact that there is some information available on how that might be interpreted.

All right, let us deal first with the blood levels, and do you want me to go through calculations or just give you numbers? It is basically the same kind of calculations we did this morning, which is the maximum and minimum amounts which would have to be administered to produce a level of, say, 78 or whatever number we are going to take. We will arbitrarily use 78. There are some differences among the different samples, but we will accept 78 as the number.

Q. All right, why do you not give us the maximum and minimum, and if we are so shocked by either of them that we need some explanation we will seek it from you.

EE2

A. Fine. The minimum, again, assuming administration at the time all circulation ceased, which I do not think is a good possibility in this situation for reasons we will get into, but we have to state the minimum, would be about 15 micrograms of digoxin. This is again a fraction of one pediatric vial, about a third of a pediatric vial.

The central volume of distribution, which is that little knee in the graph that we looked at before, which would happen, say, minutes after administration, we are talking about amounts ranging about 380 micrograms. Now, this is less than one adult vial, but do not get me wrong. This is a tremendous amount of digoxin for a child this size.

Q. Sorry, what was the amount again?

A. 387 micrograms of digoxin.

THE COMMISSIONER: What is that figure?

THE WITNESS: This would be the figure which would occur several minutes after administration, assuming that the drug has now left serum and entered this space which we really cannot define anatomically, the central volume of distribution.

EE3

THE COMMISSIONER: I am sorry, I do not understand. You say the minimum that could have been injected into this child was 15 micrograms, which is one-third ---

THE WITNESS: That would be the minimum that could produce a level of 78 nanograms per ml.

THE COMMISSIONER: Yes, all right. What is the 387?

THE WITNESS: 387 would be -- let me draw it again.

THE COMMISSIONER: No, just tell me what it is, that is all.

THE WITNESS: Okay. What it is is the knee in that curve, the central volume of distribution, the amount of digoxin necessary to produce a level of 78 nanograms per ml several minutes after administration when the drug has left serum and has entered that central volume. Now it has to distribute with a half life of 30 minutes down that curve down to the steady state.

THE COMMISSIONER: I thought the question was what was the minimum and what was the maximum; was that not the question?

THE WITNESS: The issue is that we

EE4

are going to have to discuss each of -- we are going to have to discuss really three to make it intelligent and to make it pharmacologically valid.

THE COMMISSIONER: Yes, all right.

THE WITNESS: The final volume of distribution, then, at 15 litres per kilogram and now we are talking at least two and a half hours after administration, perhaps more, as we discussed, would be 5.8 milligrams, and in ampules here we are talking perhaps 12 adult ampules and perhaps again, you know, the 120 pediatric ampule example.

THE COMMISSONER: Well, you are not making it any easier for me, and I suppose if you have to draw it, you have to draw it. I just was hoping that we could get a quick answer to a simple problem.

First of all, you can explain afterwards, but the first question was what is the minimum dosage?

THE WITNESS: The minimum is 15 micrograms; the maximum is 5.8 milligrams.

THE COMMISSIONER: All right, thank you.

MR. LAMEK: Q. And the first of those, the minimum, Dr. Spielberg, is on the basis of administration at the moment when circulation ceased.

A. Presumably at a time when no

E5

distribution occurs.

Q. And what would be an equivalent of a third of a pediatric vial?

A. Right.

Q. The other presupposes steady state distribution and is the equivalent of 12 adult ampules and 120 of the pediatric ones?

A. Exactly, and the most likely hypothesis is the aforestated in between value which we have to get back to.

Now, the trouble with the 15 microgram theory is that we have appreciable quantities of digoxin in tissue. Therefore, we cannot, in good conscience, accept that as a reasonable amount of digoxin to have been administered because, in fact, we do have evidence of digoxin within tissues. So the amount clearly has to be more than that.

Q. You are thinking in particular, I take it, of the 1177 nanograms per gram measured in the heart?

A. Yes. Now, we have, and again, we cannot really deal with the fixed tissues because the fixed tissues in this situation are terrible representation of the fresh tissues, so that we really just do not know what to make of it. But we

EE6

do have some fresh data, and again, assuming that the 1100 in the heart is correct, and assuming that the concentration in liver, and I am sorry I do not have ---

Q. The other was in lung, Dr. Spielberg, fresh lung 153.

A. Yes, okay. Those concentrations are reasonably sizeable concentrations of digoxin and, as such, I think it is implausible to accept that minimum amount.

Q. Because, I take it, the blood must have remained in circulation long enough after the dose to transport that amount of digoxin to those organs?

A. This would seem reasonable. So that the very minimum amount, I think, becomes very, very much less likely.

Now, what about the maximum amount? This is the 12 ampules and the 120 ampules. I think this, too, in this baby is extremely unlikely. Let us first look at the clinical circumstances of this child. This child has a clinical heart disease that would be made potentially worse by digoxin. The problem is he has pulmonary out flow of struction and if you increase force of contraction

EE7

in such a patient, the patient may get worse. So that clinically for him to have survived the entire time period of distribution of those kinds of levels into tissue seems very, very unlikely.

The second point is the simple physical handling of these kinds of things. To open 120 vials of pediatric digoxin takes tremendous effort and tremendous time, and physically seems rather unlikely. 12 ampules of adult digoxin is 24 ml, 24 millilitres of digoxin. Again, it takes a great deal of time to open 12 ampules. They have to be snapped open. Then you have to draw up each sample. It is a very time dependent process.

Then once you have a syringe, if you can find a syringe large enough -- as far as I am aware, most of the syringes available were 20 milli-litre syringes on the ward is the largest size, so you would have to find a syringe some place that were larger and be able to carry such a vehicle around, you then have 24 millilitres in a very large syringe, which you then have to administer in some way. If you began trying to push this volume, which would be reasonably rapidly injected through the small kinds of needles used in pediatrics, the IV would never stand up against the pressure. It would take you a very

EE8

long time, indeed, to push in that, and if you could push that volume in fast enough, the child, in all likelihood, would end up arresting from fluid over-load prior to the time that you got the digoxin into the patient.

There are some other reasons as well, but I think that gives you the flavour of why it seems unreasonble to think in terms of those large numbers of vials.

However, there is a middle ground, obviously, between these vast large concentrations and the very tiny minimum concentration, and that is what I was trying to get at, Mr. Commissioner, with the issue of the central volume of distribution, after it comes out of plasma and now into a central volume from which it then ends up distributing.

The kinds of concentrations or amounts required to produce those sorts of numbers, assuming 78 being correct, would be in the neighbourhood of 380 micrograms. This is less than one adult vial of digoxin. Now again, an adult vial of digoxin given to an infant the size of Justin Cook is a very large excess of digoxin. We cannot minimize that if that amount of digoxin were given to the child that it is trivial; it is not. It comes out

somewhere in the neighbourhood of 80 micrograms per kilogram. This is more than twice a loading dose that might be used, and a loading dose is normally given in breakdown doses over a 24 hour period. So that this is still a large amount of digoxin.

If the child received this, one might well expect that if circulation continued for a period of time either during the arrest and resuscitation or immediately before, that tissue concentrations might well reach the kind of tissue concentrations that we are talking about. Again, with the tremendous inter-individual variability and everything else, one cannot say for sure, trying to back calculate from 1100 in the heart to the amount given, we do not really know whether that is specifically boundage or non-specifically bound drug because of the acute nature of the phenomenon that we are looking at. We are looking at probably reasonably short periods of time. But we can be reasonably confident, assuming that those numbers are correct, the child received a large dose of digoxin at some point prior to or during his arrest.

THE COMMISSIONER: Sorry, I am having trouble again. I would have thought that if he were to receive the dose immediately prior to his

EE10

arrest, presumably at that point the circulation would cease or pretty well cease?

THE WITNESS: He reachieved some circulation during that period of time, which is the thing that we cannot really deal with. For a brief period of time after he was defibrillated, he apparently did go into some dysrhythm and circulation will continue, albeit not maximal or not very well.

The problem is we only have tissue levels in lung and heart and that as was suggested if the dose were perhaps given intra-cardiac, that dose would distribute to the lung and the heart preferentially and in the absence of a lot of information in other organs, it makes it very difficult to say much more than that. The blood injected would have gone first to lung, back to the heart, into the left ventricle, distributing to the coronary arteries, which would then have taken it into the heart. So that one might have gotten a situation with a few pumps on the chest during the resuscitation plus a brief period of re-establishment of circulation, enough distribution to have achieved that, particularly since we are not talking about trivial amounts of digoxin. We are talking about a reasonably large amount of digoxin, in fact.

EE11

Now, the question, then, comes down to how that digoxin got there. We have no corroborating evidence that helps us one way or the other to answer the question.

The two possibilities are somebody intentionally gave this baby an overdose of digoxin. That has to be accepted as a possibility. The other possibility, as we suggested before, is that this baby received an inadvertent dose of digoxin.

How can we begin trying to approach separating these things? If we were talking about 12 vials of this and 120 vials of that, there is no question but that this would have had to be intentional. We could have ruled out the issue altogether, and that is why we had to go through the pharmacological exercise. There is no way that somebody is going to stand and open 12 vials of digoxin and give it accidentally.

If this is a single vial of digoxin, then we are left just in a pharmacological sense at a breakpoint between trying to decide likelihood of intent or unintentional administration. How can we work out this further?

Now, Justin Cook's death occurred after a series of events had occurred within the

EE12

Hospital.

Again, since I was not here at the time, I do not have all of the details and I have not really had the opportunity to review all of the testimony.

My understanding is that recognizing that there might have been a problem with digoxin on the ward, an attempt was made to collect the digoxin which was then available on the ward and to basically keep it as a restricted drug under lock and key, so that an attempt was made to remove digoxin's availability. On the one hand, this would suggest that if no digoxin indeed were available on the ward through traditional mechanisms, then one would have to argue that some way the baby was given the digoxin through non-traditional mechanisms.

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Now, the probability of no digoxin being on the ward, which, I mean to say, no digoxin, has to at least be questioned somewhat, again, from experience of the similarity of vials and the situation on the ward at the time.

I think the possibility at least exists and has to be considered that, in the frenzy, number one, of trying to remove all the digoxin, some may have been missed.

Is this impossible? Not in the least, in my mind, given what happens when these events are occurring in a complex and, at that time, rather sad ward. Looking for all the digoxin and trying to make sure there is none there, a vial conceivably could have been missed.

If a vial were missed under those circumstances, the probability of a medication error goes up dramatically in this child because the expectation is that there is not going to be any digoxin around. Therefore, when one looks down at labels which are written in extremely small sizes and which, frankly, I - and I know of no other physician who has not misread some labels, particularly at the time of an arrest. If some digoxin were around, the probability of an error is increased because

FF2

no one expected it to be there.

THE COMMISSIONER: Well, I'm not absolutely sure about that, doctor. Certainly, those who went around collecting didn't expect it to be there. I am not sure this was known to everyone at the time.

THE WITNESS: I honestly don't know. I honestly don't know. I don't know, for example, if the nursing shift that was going on knew that the digoxin had been locked up. I assume they would have had to because they would have had to get it out from under lock and key.

THE COMMISSIONER: If the only medical error was digoxin, we would naturally be concerned and make sure we are not doing digoxin but, presumably, the medical error is possible at any time.

THE WITNESS: That is correct.

THE COMMISSIONER: So it wouldn't, the fact there was no digoxin around, wouldn't in any way reduce their vigilence to make sure they are not making an error, would it? They wouldn't want to make an error and give cocaine or something instead, or cyanide.

THE WITNESS: The issues are really

FF3

basically the medications that come in similar kinds of vials and tend to be on specific wards at specific times.

THE COMMISSIONER: We have had that and, no doubt, we will have some more of it. At any rate, you say that it could have been there?

THE WITNESS: It is, again, from things that we have experienced, again, mostly in other institutions.

MR. LAMEK: Q. Dr. Spielberg --

THE WITNESS: It is a probability but how much of a probability it is as opposed to an intentional administration, I can't say and, obviously, it is going to have to be up to the Commission to say.

Q. Forgive me.

A. Yes.

Q. Could I let you know what the evidence has been here in that regard.

I do not want to take you beyond the area of your expertise as a clinical pharmacologist as to the likelihood of accidental administration happening given certain circumstances.

The evidence here has been that, on the evening of March 21st, Drs. Costigan and

FF4

Mountsteven took an inventory of the parentaral digoxin preparations and, in particular, checked crashcarts. On the following day, Miss Rappaport also did an inventory and, indeed, she found some digoxin where the two doctors the previous evening had not found it.

The clear evidence of Dr. Costigan here was that they found no digoxin on the crash carts on 4A/B and the inventory that they prepared on the Saturday evening exactly coincides with that made by Miss Rappaport the following morning with respect to the parentaral preparations on the ward. So, if there was some digoxin missed somewhere, either it was used up in the way you are perhaps suggesting it may have been in the course of the night or Miss Rappaport missed it too the following morning. To the extent that counts were taken, that is the evidence that has been here so far.

A. The other thing, of course, and, again, not really knowing about the drug administration system in depth, is that, during that time, I believe there has also been evidence that other medicines were borrowed from other wards as things ran out - for instance, propanolol and other medicines. Again, that is a potentially error prone

FF5

type of situation.

I think we have to recognize that Justin Cook received somewhere in the neighbourhood of 25 intravenous medications from the time - and that is an estimate; it may be a little bit higher or lower, but that is what I have down from my previous notes. From the time of his initial blue spell at 1800 hours on the 21st through the end of his arrest, this baby had a heroic attempt made at trying to resuscitate him - every effort possible was made. Many, many, many different medications were administered and I think one has to at least accept the possibility that,of all those things, something was missed along the way.

The other thing that is of interest in his chart with respect to what appears in charts and what appears afterwards is something that I don't have a good explanation for, really, and is not anything that one, I think, would view as malevolant. There is another drug found in the baby that was not in the chart, and that drug is lidocaine. Now, there is a reason that one might want to give lidocaine to this baby. Lidocaine is used to decrease the irritability of the heart and to decrease certain types of arrhythmias of the heart. It is interesting

FF6

that despite an extremely detailed arrest sheet on this infant, the lidocaine simply is not charted. I don't mean to imply that somebody was trying to overdose the child with lidocaine; in fact, the concentrations were therapeutic, but only to point out that medication administration during an arrest even if somebody is keeping a good record - and this is an exemplary resuscitation record - even under those circumstances, medications administered to a child are sometimes missed and not recorded.

Again, resuscitation, the events surrounding them, unless you have been at them, particularly at night when your backup staff is very limited, are phenomenally complicated events, tremendous pressure, and I can only imagine what the pressure was like when the doctors and nurses were trying to resuscitate this infant in light of everything that had occurred in the previous few days.

Q. Dr. Spielberg, could you turn with me to page 30 of the Cook chart, please.

A. Yes.

Q. The number in the top right-hand corner, and the page I have in mind also has beneath the 30, a 15.

A. Yes.

FF7

Q. But it records the drugs administered in the course of the resuscitation efforts.

A. Yes.

Q. Notwithstanding that the time 4:20 appears to be that at which the arrest was called, certain drugs were administered prior to that because the baby started getting in trouble about 3:55, you will recall.

A. Right.

Q. Now, I see three drugs on that page which appear to have been administered directly into the heart. Half-way down the page there is a notation, I take it, of adrenalin.

A. Intercardiac adrenalin.

Q. 1cc.

A. Intercardiac calcium.

Q. 4:50, intercardiac adrenalin, 3cc.

A. Right.

Q. And at 4:53, intercardiac calcium.

A. Correct.

Q. 3cc.

A. That's correct, yes.

FF8

Q. Now, I confess I get rather confused and puzzled here because some of these doses are expressed in cubic centimetres and others in milligrams and so on.

We are talking of a dose of what size? Let's take your middle ground.

A. Okay. Again, recognizing that it is a guessestimate --

Q. Yes.

A. -- 300 to 400 micrograms.

Q. You are more adept at this than I. Could you translate that into either millgrams or cubic centimetres for me.

A. Okay. In terms -- this is assuming pure adult strength digoxin, okay. If this was adult strength digoxin, we would be talking in the neighbourhood of 1.5 cc. of adult strength digoxin, that neighbourhood. For pediatric strength, you would have to multiply it by 10.

Q. In terms of vials of less than 1, 2.5 cc. is the size of the vials?

A. It is 2 cc.

Q. 2cc.?

A. An adult vial is 2cc.

Assuming a 2 cc. vial could

FF9

conceivably explain both the intracardiac levels, the lung levels and the serum levels which we see in the baby.

Q. Okay. But a 2 cc. vial would not, I take it, have been confused with either the administration at 4:50 or 4:53, each of which were 3 cc.

A. Well, again --

Q. You would need to make the mistake twice, I guess.

A. The problem is the adrenalin.

Q. Yes.

A. And some of the other medicines which were then used on the crash carts. Adrenalin is prepared at that time. It was not in prepackaged syringes, as it is today. It came as a vial which you had to crack open, draw up into a syringe and then you had to enter a second vial of normal saline to dilute the epinephrine. In other words, the epinephrine on the carts was concentrated epinephrine, and you don't give it in that form; you have to make a preparation of it. This takes time and, often, I remember as a house officer facing these kinds of situations, it can be very confusing and, particularly, in an urgent situation. You have

FF10

to draw up the vial and then you have to draw up the saline in addition.

Q. When I see a reference to adrenalin, 3cc., is that 3cc. of the diluted?

A. That would have been the diluted form. In fact, it almost would have to be the diluted form.

Q. And what is the amount of adrenalin, that 3cc. administered dose?

A. It would be about, oh, the equivalent - again, it is a guess, depending on how much they diluted it. It would probably be between, in the neighbourhood of .5 cc., a third, probably about .3cc. of epinephrine to perhaps as much as .6cc. of concentrated epinephrine, depending on how they actually diluted it.

The typical solution would be a 1 to 10, which would mean 1 cc. of adrenalin drawn up to 10 cc. But some people dilute it differently, and I honestly don't know what was going on at that time. In which case, if they gave 3 cc. of the diluted form, that would be the equivalent of .3 cc. of concentrated epinephrine. If they diluted it less, it would be proportionately more, of course.

Q. Do I take it, therefore,

FF11

that had they drawn up, instead of .3 cc. of epinephrine, .3 cc. of digoxin, they would not have had the volume of digoxin necessary to produce the levels, according to your data?

A. Hard to know.

Q. Your data suggested a higher volume than that.

A. Yes. Now, the problem is that the vials, in one case, contain 2 cc. and, in another case, contain 1 cc. The epinephrine being 1 cc. and the digoxin adult strength being 2 cc.

In an urgent situation, you can't tell the difference between 1 cc. and 2 cc.

Q. Are there not calibrations on the --

A. What you would be doing is you would draw up a whole vial. The physician asking the nurse to do it says, "Give me an amp. of epinephrine.", he doesn't say, "Give me 1 cc. of epinephrine". The nurse cracks open the amp., draws up the whole amp., draws it up in normal saline to whatever mark she is instructed to, and it is given.

Q. What type of syringe were you using?

A. 10 cc. syringe, okay.

FF12

Q. All right.

A. So the difference between drawing up 1 cc. and 2 cc. and then adding 8 or 9 cc. of saline, it is unlikely that you would notice it, particularly during an arrest.

That is why we now have preloaded epinephrine - too many mistakes used to be made with it, and that is why we now have 10 cc. syringes containing a 1 to 10,000 dilution of epinephrine.

Q. Okay. Let's assume for a moment - and we are getting very close to the end of the day and, actually, we are playing overtime at the moment; we are on injury time. Let's assume for the moment the possibility of administration by intra-cardiac injection in the course of this arrest, in the course of this resuscitation. The first intra-cardiac injection was at 4:32.

A. Yes.

Q. And the arrest was stopped at 4:56.

A. Oh, I'm sorry, yes, correct. It is about --

Q. 25 minutes.

A. 24 minutes, yes.

Q. Would that period of time,

FF13

in those circumstances, account, in your judgment, for the concentrations of digoxin found in the fresh tissue of this child?

A. I cannot give you a hard answer on it, okay, because, again, of the variabilities. If it was put directly into the heart and there was adequate circulation to get it from the heart to the lung back to the coronary circulation, yes, possibly.

Can I put a qualifier on it?

Q. And, indeed, into the serum itself?

A. Yes. Well, we are saying that a lot of it is sitting exactly there; it enters the serum instantaneously upon injection.

Q. Wait a minute. I thought we were injecting it into the heart. Are we injecting it into the blood inside the heart, into the heart tissue?

GG-1

A. When people talk about intra-cardiac medications it is into the cardiac blood.

Q. All right.

A. Not into the heart muscle.

Q. Well, piercing the muscle and going right through ---

A. Going through the myocardium often drawing back slightly until one enters the chamber of the heart, seeing blood flow back and then administer the drug.

Q. All right. So, we do then have to get from blood not only into the heart in the concentrations noted but also into lung, as you have said?

A. Yes.

Q. And you say you cannot tell me with any confidence whether in the space of 24 minutes in this circumstance that would have happened?

A. I think it is pharmacologically very reasonable. I cannot give you any hard data to back it one way or the other.

Q. You are, if not familiar with, I take it you know of Dr. Ralph Kauffman?

A. Yes.

Q. Who I gather is a clinical

GG.2

pharmacologist of some distinction?

A. Yes.

Q. And you are aware of his involvement in assisting the Metropolitan Toronto Police in this matter?

A. Yes.

Q. And subsequently the Centres for Disease Control?

A. Yes.

Q. Dr. Kauffman on the scoring system that he was using scored this death, that of Justin Cook, a 5, that is to say consistent with special conern with respect to digoxin toxicity?

A. Yes.

Q. And I take it, Doctor, that you would agree with that assessment?

A. I think it is impossible not to by those criteria because there is evidence of an excessive amount of digoxin in this baby and there is no other reasonable explanation that we have except for administration. Therefore, we have to be concerned about it. We have to be terribly concerned about it. The problem from my standpoint pharmacologically is that I cannot rationally separate out the mechanism by which the digoxin

GG.3

arrived there. I know a great deal about medication errors. These are frequent events. I know very little about murder. I cannot on the pharmacologic evidence separate them except to say that errors occur frequently, murder occurs rarely. It is very reasonable to mean that this could have been an error despite the locking up of the digoxin and everything else. I think it is a very reasonable hypothesis in this particular child.

MR. LAMEK: Okay. We may leave it there for today, Mr. Commissioner.

THE COMMISSIONER: Yes, all right. 10 o'clock tomorrow morning.

MR. LAMEK: Thank you.

--- Whereupon the Hearing was adjourned at 4:35 p.m. until Tuesday, October 25th, 1983 at 10:00 a.m.

[illegible] theory. I know a great deal about medication [illegible]. These are frequent events. I know very little [illegible] murder. I cannot on the [illegible] evidence eliminate [illegible] that [illegible] frequently [illegible]. It is very [illegible] to [illegible] that [illegible] would [illegible] the [illegible] of the [illegible] and [illegible]. I think it is a very [illegible] of [illegible].

MR. [illegible]: [illegible]. We may leave it [illegible] for today, Mr. Commissioner.

THE COMMISSIONER: Then, all right, we'll adjourn [illegible].

MR. [illegible]: Thank you.

The [illegible] were adjourned at [illegible] p.m. [illegible] at 10:00 a.m.